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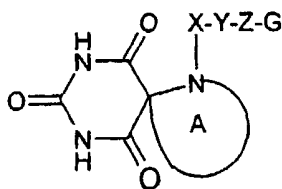
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(54) Title: SPIRO-PYRIMIDINE-2,4,6-TRIONE METALLOPROTEINASE INHIBITORS



(57) Abstract: The present invention relates to 5-spiro-pyrimidine-2,4,6-trione metallo-
proteinase inhibitors of the formula wherein said "A" is a 5-7 membered heterocyclic ring
as defined in the specification and to pharmaceutical compositions and methods of treating
(i) inflammation, cancer and other disorders.

SPIRO-PYRIMIDINE-2,4,6-TRIONE METALLOPROTEINASE INHIBITORS**Background of the Invention**

The present invention relates to 5-spiro-pyrimidine-2,4,6-trione metalloproteinase inhibitors and to pharmaceutical compositions and methods of treatment of inflammation, cancer and other disorders.

The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the class of matrix metalloproteinases (also called MMP or matrixin).

The MMP subfamily of enzymes, currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMP's are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and differentiation. In addition, the MMP's are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, *et al.*, *J. Clin. Invest.*, 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMP's is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

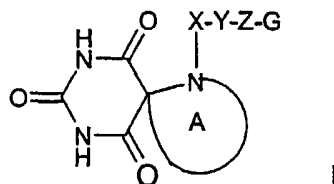
It is recognized that different combinations of MMP's are expressed in different pathological situations. As such, inhibitors with specific selectivities for individual MMP's may be preferred for individual diseases.

Matrix metalloproteinase inhibitors are well known in the literature. Hydroxamic acid MMP inhibitors are exemplified in European Patent Publication 606,046, published July 13, 1994. Several pyrimidine-2,4,6-trione MMP inhibitors are referred to in PCT publication WO 98/58925, published December 30, 1998. PCT publication WO 00/47565, published August 17, 2000 refers to certain aryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Non-provisional application 09/635156, filed August 9, 2000 (which claims priority to United States Provisional application 60/148547 filed August 12, 1999) refers to heteroaryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Provisional Application entitled "Pyrimidine-2,4,6-trione Metalloproteinase Inhibitors", filed October 26, 2000, refers to certain pyrimidine-2,4,6-triones. Barbituric acids and methods for their preparation are well known in the art, see for example Goodman and Gilman's, "The Pharmacological Basis of Therapeutics," 345-382 (Eighth Edition, McGraw Hill, 1990). Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

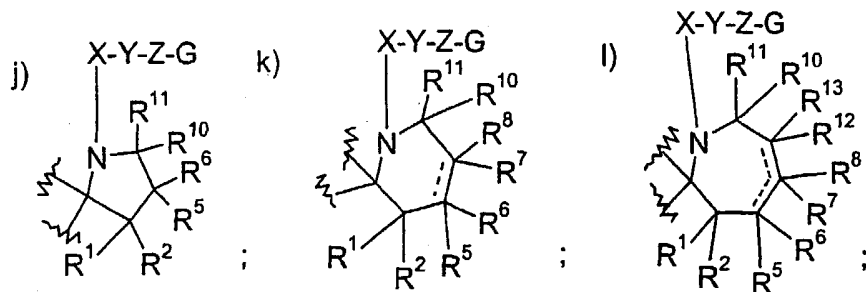
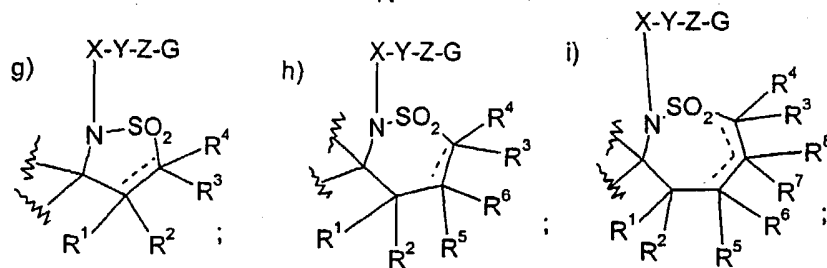
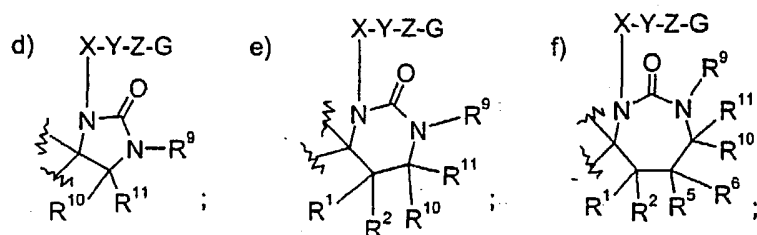
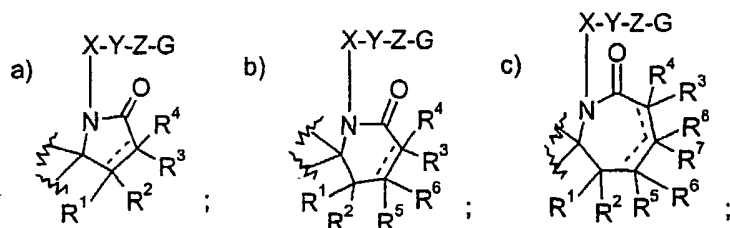
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Summary of the Invention

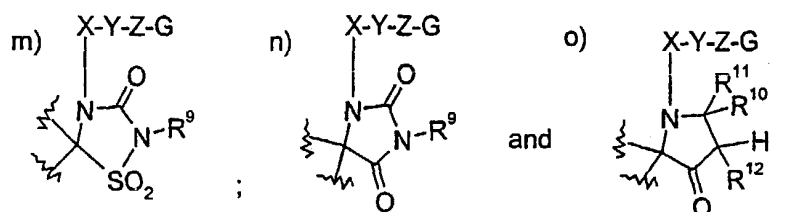
The present invention relates to compounds of the formula:



wherein said "A" is a 5-7 membered heterocyclic ring selected from the group consisting of:



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wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl;
 5 wherein each of said (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond with 1-3 substituents per ring independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -CN, -OH and -NH₂;

X is (C₆-C₁₀)aryl or (C₁-C₁₀)heteroaryl;

10 Y is selected from the group consisting of a bond, oxygen, sulfur, >C=O, >SO₂, >S=O, -CH₂-, -CH₂O-, -O(CH₂)_n-, -CH₂S-, -S(CH₂)_n-, -CH₂SO-, -CH₂SO₂-, -SO(CH₂)_n-, -SO₂(CH₂)_n-, -NR¹⁴-, -NR¹⁴(CH₂)_n-, -CH₂[N(R¹⁴)]-, -CH₂(CH₂)_n-, -CH=CH-, -C≡C-, -[N(R¹⁴)]-SO₂- and -SO₂[N(R¹⁴)]-;

n is an integer from one to four;

15 R¹⁴ is hydrogen or (C₁-C₄)alkyl;

Z is selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heterocyclyl and (C₁-C₁₀)heteroaryl; wherein one or two carbon-carbon single bonds of said (C₃-C₈)cycloalkyl or (C₁-C₁₀)heterocyclyl may optionally be replaced by carbon-carbon double bonds;

20 wherein each of said X or Z may be independently optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy;

25 G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein G is a substituent on any ring carbon atom of Z capable of forming an additional bond and is oriented at a position other than alpha to the point of attachment of the Z ring to Y;

p is an integer from 0 to 4;

30 R¹⁵ is independently selected from the group consisting of halo, -CN, -NO₂, OH, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)perfluoroalkyl, perfluoro(C₁-C₄)alkoxy, R¹⁸-, R¹⁸-O-, R¹⁸-(C₁-C₄)alkyl-O-, R¹⁸-(C=O)-, R¹⁸-(C=O)-O-, R¹⁸-O-(C=O)-, R¹⁸-S-, R²²-(S=O)-, R¹⁸-(SO₂)-, R²²-(SO₂)-(NR²¹)-, R¹⁹-(C=O)-(NR²¹)-, R²²-O-(C=O)-(NR²¹)-, (R¹⁹R²⁰)N-, (R¹⁹R²⁰)N-(SO₂)-, (R¹⁹R²⁰)N-(C=O)-; (R¹⁹R²⁰)N-(C=O)-(NR²¹)- and (R¹⁹R²⁰)N-(C=O)-O-;

each of R¹⁶ and R¹⁷ is independently selected from hydrogen and (C₁-C₄)alkyl;

or R¹⁶ and R¹⁷ may optionally be taken together with the carbon to which they are attached to form a 5 to 10-membered carbocyclic ring;

R¹⁸, R¹⁹, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

or R¹⁹ and R²⁰ may optionally be taken together with the nitrogen to which they are attached to form a 3 to 8-membered heterocyclic ring;

or R¹⁹ and R²¹ may optionally be taken together with the nitrogen, the carbon or the oxygen to which they are attached to form a 3 to 8-membered heterocyclic ring;

R²² is selected from the group consisting of (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

or R²¹ and R²² may optionally be taken together with the nitrogen, the oxygen or the sulfur to which they are attached to form a 3 to 8-membered heterocyclic ring;

or the pharmaceutically acceptable salts thereof.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate,

tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, *para*-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that
5 may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (*e.g.*, potassium and sodium) and alkaline earth metal cations (*e.g.*, calcium and magnesium), ammonium or water-
10 soluble amine addition salts such as N-methylglucamine (meglumine) and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The term "a bond", as used herein in the group Y, means that the groups X and Z are directly connected through a carbon-carbon bond so as to form pendent aryl rings such as diphenyl.

15 The dashed lines as used in each of the heterocyclic ring "A" of formulae a), b), c), g), h), i), k) and l) refer to optional double bonds. The exact positions of the optional double bonds for each of the heterocyclic ring "A" of formulae a), b), c), g), h), i), k) and l) are as defined in the specification. Whenever the dashed line extends over two carbon atoms, one skilled in the art will understand that two carbons are tetravalent and that the extra
20 substituent(s) (*i.e.*, any of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹⁰, R¹¹, R¹², or R¹³) may be absent.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched moieties, or combinations thereof. Alkyl groups, wherever they occur, may be optionally substituted by a suitable substituent.

25 The term "alkenyl", as used herein, unless otherwise indicated, includes hydrocarbon radicals containing at least one olefin linkage and having straight, branched moieties, or combinations thereof.

The term "alkynyl", as used herein, unless otherwise indicated, includes hydrocarbon radicals containing at least one carbon-carbon triple bond linkage and having straight, branched moieties or combinations thereof.

30 The term "cycloalkyl", as used herein, unless otherwise indicated, includes a mono or bicyclic carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro,
35 chloro, trifluoromethyl, (C₁-C₄)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₄)alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

5 The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one or more hydrogens, such as phenyl or naphthyl, optionally substituted by 1 to 3 suitable substituents such as fluoro, chloro, cyano, nitro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, (C₃-C₈)cycloalkyloxy, trifluoromethoxy, difluoromethoxy, or (C₁-C₆)alkyl.

10 The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one or more hydrogens, such as benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, indoliziny, indolyl, 3H-
15 indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently
20 selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy. The foregoing groups, can be C-attached or N-attached where such is possible. For instance, pyrrolyl can be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

25 The term "heterocyclyl", as used herein, unless otherwise indicated, includes an organic radical derived from a non-aromatic heterocyclic compound by removal of one or more hydrogens, such as 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidiny, dihydrofuranyl, dihydropyranyl, dihydrothienyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydroazepinyl, hexahydropyrimidine, imidazolidinyl, imidazoliny, isoxazolidinyl, morpholinyl, oxazolidinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl,
30 pyrazolinyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, quinoliziny, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl and trithianyl. The foregoing groups, can be C-attached or N-attached where such is possible. For example, piperidinyl can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached). The foregoing groups, as derived from the compounds listed above, can be
35 optionally substituted where such is possible by a suitable substituent, such as oxo, F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, or (C₃-C₈)cycloalkyloxy.

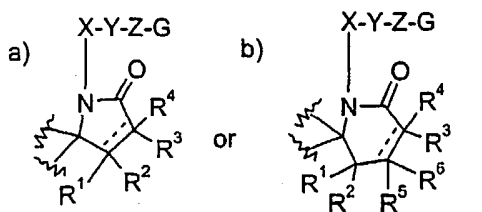
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The phrase "a suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group *i.e.*, a moiety that does not negate the inhibitory activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, carboxy groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxy carbonyl groups, alkylaminocarbonyl groups, dialkylamino carbonyl groups, arylcarbonyl groups, aryloxy carbonyl groups, alkylsulfonyl groups, an arylsulfonyl groups and the like.

The phrase "at a position other than alpha to the point of attachment of the Z ring to Y", as used herein, unless otherwise indicated, is intended to mean a chemically and pharmaceutically acceptable orientation of the bond connecting group Z to G (Z-G bond) relative to the bond connecting group Y to Z (Y-Z bond). Such relative orientation may be *meta*, wherein the Z-G bond is in the 1,3 position relative to the Y-Z bond. Another relative orientation may be *para*, wherein the Z-G bond is in the 1,4 position relative to the Y-Z bond.

Some compounds of formula I contain chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, enantiomers, diastereomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of the invention also exist in different tautomeric forms. This invention relates to all tautomers of formula I. Those skilled in the art are well aware that the pyrimidine-2,4,6-trione nucleus exists as a mixture of tautomers in solution. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular crystallization technique used to isolate a compound.

In one embodiment of the invention, the heterocyclic ring "A" of the compounds of the formula I is selected from the formulae a) or b):



wherein X is (C₆-C₁₀)aryl, preferably phenyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, >C=O, -CH₂-, -CH₂O-, -O(CH₂)_n-, -CH₂CH₂-, -CH=CH- and -C≡C-; wherein n is 1 or 2; preferably Y is selected from the group consisting of oxygen, -OCH₂- and -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formulae a) or b), wherein X is (C₆-C₁₀)aryl, preferably phenyl. Within this embodiment, Y is selected from

the group consisting of sulfur, $>\text{SO}_2$, $>\text{S}=\text{O}$, $-\text{CH}_2\text{S}-$, $-\text{S}(\text{CH}_2)_n-$, $-\text{CH}_2\text{SO}-$, $-\text{CH}_2\text{SO}_2-$, $-\text{SOCH}_2-$ and $-\text{SO}_2(\text{CH}_2)_n-$; wherein n is 1 or 2; preferably Y is sulfur or $>\text{SO}_2$.

In another embodiment of the invention, the heterocyclic ring "A" has the formulae a) or b), wherein X is $(\text{C}_6-\text{C}_{10})$ aryl, preferably phenyl. Within this embodiment, Y is selected from the group consisting of $\text{CH}_2[\text{N}(\text{R}^{14})]-$, $>\text{NR}^{14}$, $-\text{NR}^{14}(\text{CH}_2)_n-$, $-\text{SO}_2[\text{N}(\text{R}^{14})]-$ and $-\text{N}(\text{R}^{14})-\text{SO}_2-$,
 5 wherein R^{14} is hydrogen or methyl; and n is 1 or 2.

In another embodiment of the invention, the heterocyclic ring "A" has the formulae a) or b), wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl,
 10 benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolyl, quinolyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said $(\text{C}_1-$
 15 $\text{C}_{10})$ heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy and (C_3-C_8) cycloalkyloxy; preferably X is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably
 20 X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably X is pyridinyl. Within this embodiment, Y is a bond, oxygen, sulfur, $-\text{CH}_2-$, $>\text{SO}_2$, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; preferably Y is oxygen, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formulae a) or b), wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl,
 25 benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolyl, quinolyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said $(\text{C}_1-$
 30 $\text{C}_{10})$ heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy and (C_3-C_8) cycloalkyloxy; preferably X is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably
 35 X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of sulfur, $>\text{SO}_2$, $>\text{S}=\text{O}$, $-\text{CH}_2\text{S}-$, $-\text{S}(\text{CH}_2)_n-$

, $-\text{CH}_2\text{SO}-$, $-\text{CH}_2\text{SO}_2-$, $-\text{SOCH}_2-$ and $-\text{SO}_2(\text{CH}_2)_n-$; wherein n is 1 or 2; preferably Y is sulfur or $>\text{SO}_2$.

In another embodiment of the invention, the heterocyclic ring "A" has the formulae a) or b), wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolyl, quinolyl, quinoxalyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said $(\text{C}_1-\text{C}_{10})$ heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy and (C_3-C_8) cycloalkyloxy; preferably X is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably X is pyridinyl. Within this embodiment Y is selected from the group consisting of $\text{CH}_2[\text{N}(\text{R}^{14})]-$, $>\text{NR}^{14}$, $-\text{NR}^{14}(\text{CH}_2)_n-$, $-\text{SO}_2[\text{N}(\text{R}^{14})]-$ and $-\text{N}(\text{R}^{14})-\text{SO}_2-$, wherein R^{14} is hydrogen or methyl; and n is 1 or 2.

In another embodiment of the invention, the heterocyclic ring "A" has the formula a), wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolyl, quinolyl, quinoxalyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said $(\text{C}_1-\text{C}_{10})$ heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy and (C_3-C_8) cycloalkyloxy; preferably X is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, $-\text{CH}_2-$, $>\text{SO}_2$, $-\text{OCH}_2-$ and $-\text{CH}_2\text{O}-$; preferably Y is oxygen, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; more preferably Y is oxygen.

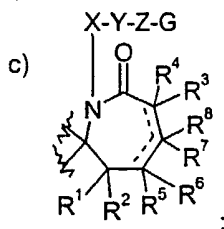
In another embodiment of the invention, the heterocyclic ring "A" has the formula a), as defined in the aforesaid paragraph, wherein in the heterocyclic ring "A" the dashed line is a double bond.

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In another embodiment of the invention, the heterocyclic ring "A" has the formula b), wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolyl, furazanyl, furopyridinyl, 5 furyl, imidazolyl, indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably X is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably X is pyridinyl. Within this 10 embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula b), as defined in the aforesaid paragraph, wherein in the heterocyclic ring "A" the dashed line is a double bond.

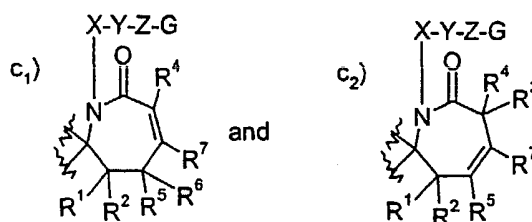
20 In another embodiment of the invention, the heterocyclic ring "A" has the formula c):



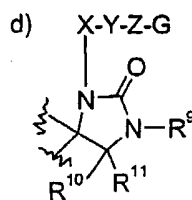
wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and 25 pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula c), wherein in the heterocyclic ring "A" the dashed line is a double bond, such that the 30 heterocyclic ring "A" of formula c is selected from the group consisting of:

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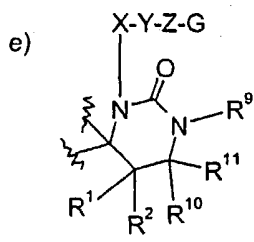


In another embodiment of the invention, the heterocyclic ring "A" has the formula d):



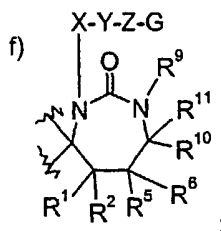
wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

10 In another embodiment of the invention, the heterocyclic ring "A" has the formula e):



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

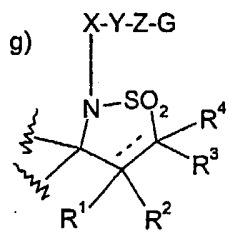
In another embodiment of the invention, the heterocyclic ring "A" has the formula f):



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wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur,
 5 -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

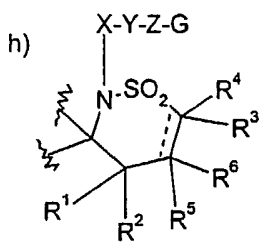
In another embodiment of the invention, the heterocyclic ring "A" has the formula g):



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl;
 10 preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

15 In another embodiment of the invention, the heterocyclic ring "A" has the formula g), as defined in the aforesaid paragraph, wherein in the heterocyclic ring "A" the dashed line is a double bond.

In another embodiment of the invention, the heterocyclic ring "A" has the formula h):

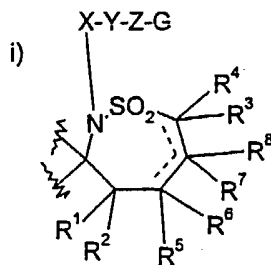


20 wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably
 25 Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula h), as defined in the aforesaid paragraph, wherein in the heterocyclic ring "A" the dashed line is a double bond.

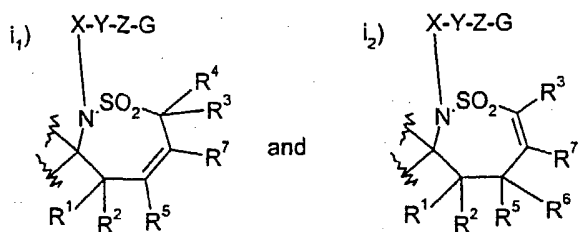
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In another embodiment of the invention, the heterocyclic ring "A" has the formula i):

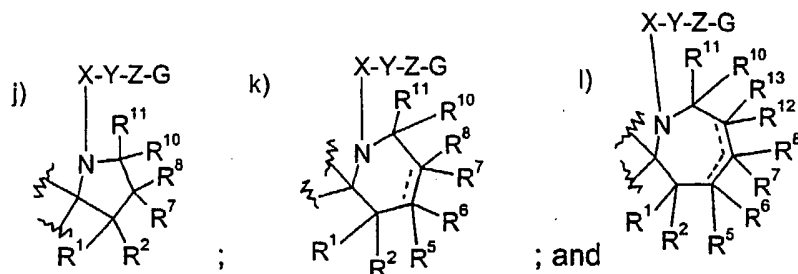


wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula i), wherein in the heterocyclic ring "A" the dashed line is a double bond, such that the heterocyclic ring "A" of formula i) is selected from the group consisting of:



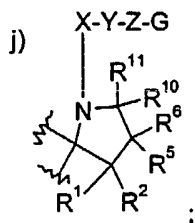
In a preferred embodiment of the invention, the heterocyclic ring "A" has the formula selected from the group consisting of



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula j):

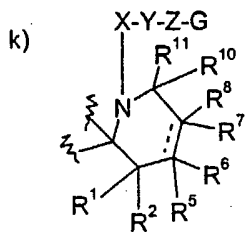
-14-



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl.

- 5 Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

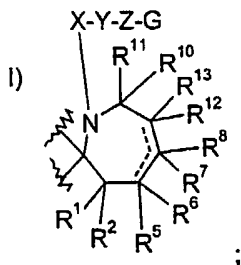
In another embodiment of the invention, the heterocyclic ring "A" has the formula k):



- 10 wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably
- 15 Y is oxygen.

In another embodiment of the invention, the heterocyclic ring "A" has the formula k), as defined in the aforesaid paragraph, wherein in the heterocyclic ring "A" the dashed line is a double bond.

In another embodiment of the invention, the heterocyclic ring "A" has the formula l):

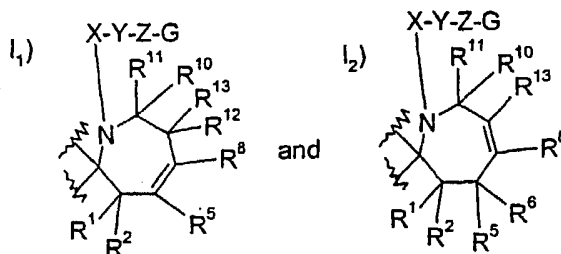


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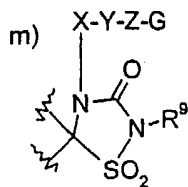
wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl;

preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, $-\text{CH}_2-$, $>\text{SO}_2$, $-\text{OCH}_2-$ and $-\text{CH}_2\text{O}-$; preferably Y is oxygen, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; more preferably Y is oxygen.

- 5 In another embodiment of the invention, the heterocyclic ring "A" has the formula l), wherein in the heterocyclic ring "A" the dashed line is a double bond, such that the heterocyclic ring "A" of formula l is selected from the group consisting of:



In another embodiment of the invention, the heterocyclic ring "A" has the formula m):

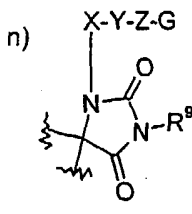


10

wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, $-\text{CH}_2-$, $>\text{SO}_2$, $-\text{OCH}_2-$ and $-\text{CH}_2\text{O}-$; preferably Y is oxygen, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; more preferably Y is oxygen.

15

In another embodiment of the invention, the heterocyclic ring "A" has the formula n):

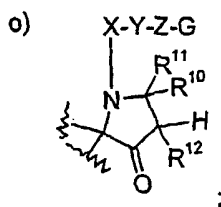


20

wherein X is $(\text{C}_1-\text{C}_{10})$ heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, $-\text{CH}_2-$, $>\text{SO}_2$, $-\text{OCH}_2-$ and $-\text{CH}_2\text{O}-$; preferably Y is oxygen, $-\text{OCH}_2-$ or $-\text{CH}_2\text{O}-$; more preferably Y is oxygen.

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In another embodiment of the invention, the heterocyclic ring "A" has the formula o):



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; preferably X is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl. Within this embodiment, Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

In another embodiment of the invention, each of R¹, R², R³, R⁴, R¹⁰, R¹¹, R¹² and R¹³ is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl; and wherein each of said (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond with 1-3 substituents independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -CN, -OH and -NH₂.

A generic or sub-generic embodiment of each of the foregoing embodiments are those compounds wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, and (C₃-C₈)cycloalkyl.

A preferred generic or sub-generic embodiment is directed to those foregoing embodiments wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ is selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

In another embodiment of the invention, each of R⁵, R⁶, R⁷ and R⁸ is selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl; and wherein each of said (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond with 1-3 substituents independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -CN, -OH and -NH₂.

In another embodiment of the invention, one or two of R⁵, R⁶, R⁷ and R⁸ is/are a group other than hydrogen.

In another embodiment of the invention, R⁸ is independently selected from hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl.

In another embodiment of the invention, R⁹ is independently selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

In another embodiment of the invention, Z is a (C₃-C₈)cycloalkyl or a (C₁-C₁₀)heterocyclyl, selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, N-methyl-3-azetidiny, piperaziny, piperidiny, 1,3-oxazolidin-4-on-5-yl, 1,3-oxazolidin-2,4-dion-5-yl, 4,5-dihydro-1,2-oxazolidin-3-on-4-yl, 1,3-thiazolidin-4-on-5-yl, 1,3-thiazolidin-2,4-dion-5-yl, 1,3-imidazolidin-4-on-5-yl, 1,3-imidazolidin-2,4-dion-5-yl, 1,2-pyrazolidin-3-on-4-yl, tetrahydro-1,3-oxazin-4-on-5-yl, tetrahydro-1,3-oxazin-2,4-dion-5-yl, morpholiny, morpholin-3-on-2-yl, morpholin-3,5-dion-2-yl, 2,3-dihydro-1,4-oxazin-3-on-2-yl, tetrahydro-1,3-thiazin-4-on-5-yl, tetrahydro-1,3-thiazin-2,4-dion-5-yl, thiomorpholiny, thiomorpholin-3-on-2-yl, thiomorpholin-3,5-dion-2-yl, 2,3-dihydro-1,4-thiazin-3-on-2-yl, hexahydro-1,2-diazin-3-on-4-yl, 4,5-dihydro-2H-pyridazin-3-on-4-yl, hexahydro-1,3-diazin-2,4-dion-5-yl, piperazin-2-on-3-yl, piperazin-2,6-dion-3-yl, tetrahydro-1,3,4-thiadiazin-5-on-6-yl, 5,6-dihydro-1,3,4-thiadiazin-5-on-6-yl, 1,3,4-oxadiazin-5-on-6-yl, 5,6-dihydro-1,2,4-oxadiazin-5-on-6-yl, tetrahydro-1,2,4-oxadiazin-5-on-6-yl, 1,2,4-triazin-5-on-6-yl, tetrahydro-1,2,4-oxadiazin-5-on-6-yl, 5,6-dihydro-1,2,4-oxadiazin-5-on-6-yl, 1,2,4-oxadiazin-3,5-dion-6-yl and 1,2,4-triazin-6-on-5-yl. Within this embodiment, preferably Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, N-methyl-3-azetidiny, piperaziny, piperidiny, N-methylpiperidiny and morpholiny. Within this embodiment, more preferably Z is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl and tetrahydropyranyl. Within this embodiment, most preferably Z is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl and tetrahydropyranyl.

In another embodiment of the invention, Z is a (C₁-C₁₀)heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiaziny, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnoliny, furazanyl, furopyridiny, furyl, imidazolyl, indazolyl, indoliny, indoliziny, indolyl, 3H-indolyl, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, naphthyridiny, oxadiazolyl, oxazolyl, phthalaziny, pteridiny, puriny, pyraziny, pyridaziny, pyridiny, pyrimidiny, pyrazolyl, pyrroly, quinazoliny, quinoliny, quinoxaliny, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triaziny and triazolyl, more preferably pyridiny, pyraziny, pyridaziny and pyrazolyl, wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy.

In another embodiment of the invention, either X or Z is substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy.

In another embodiment of the invention, both X and Z are substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy.

5 In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 0; R¹⁵ is selected from the group consisting of halo, -CN, and R¹⁸; wherein said R¹⁸ is selected from the group consisting hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms
10 capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be
15 substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-.

In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 0 to 4, preferably 1 to 2; R¹⁵ is selected from the group consisting of halo, -CN, -NO₂, OH, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)perfluoroalkyl, perfluoro(C₁-C₄)alkoxy, R¹⁸-, R¹⁸-O-, R¹⁸-(C₁-C₄)alkyl-O-, R¹⁸-(C=O)-, R¹⁸-(C=O)-O-, R¹⁸-O-(C=O)-, R¹⁸-S-, R²²-(S=O)-, R¹⁸-(SO₂)-, R²²-(SO₂)-(NR²¹)-, R¹⁹-(C=O)-(NR²¹)-, R²²-O-(C=O)-(NR²¹)-, (R¹⁹R²⁰)N-, (R¹⁹R²⁰)N-(SO₂)-, (R¹⁹R²⁰)N-(C=O)-; (R¹⁹R²⁰)N-(C=O)-(NR²¹)- and (R¹⁹R²⁰)N-(C=O)-O; each of R¹⁶ and R¹⁷ is independently hydrogen or (C₁-C₄)alkyl; R¹⁸ is selected from the group consisting hydrogen,
25 (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring
30 nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-.

35 In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 1; R¹⁵ is (R¹⁹R²⁰)N-; each of R¹⁶ or R¹⁷ is independently hydrogen; and each of R¹⁹ and R²⁰ is hydrogen or (C₁-C₁₀)heteroaryl, such as 2-oxazolyl, 2-pyrazolyl, or 3-pyrazolyl.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $(R^{19}R^{20})N-(C=O)-(NR^{21})$; each of R^{16} or R^{17} is independently hydrogen; each of R^{19} and R^{20} is (C_1-C_4) alkyl and are taken together with the nitrogen to which they are attached to form a 3 to 8-membered ring; and wherein R^{23} is selected from the group consisting of hydrogen and (C_1-C_4) alkyl.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $R^{22}-O-(C=O)-(NR^{21})$; each of R^{16} or R^{17} is independently hydrogen; R^{21} is selected from the group consisting of hydrogen and (C_1-C_4) alkyl; and wherein R^{22} is selected from the group consisting of (C_1-C_4) alkyl and (C_3-C_8) cycloalkyl, such as methyl, ethyl, propyl, butyl or cyclobutyl.

In another embodiment of the invention G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $R^{19}-(C=O)-(NR^{21})$; each of R^{16} and R^{17} is independently hydrogen or (C_1-C_4) alkyl; R^{19} and R^{21} are taken together with the carbon or the nitrogen to which they are attached to form a 3 to 8 membered heterocyclic ring.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $(R^{19}R^{20})N-(C=O)-(NR^{21})$; each of R^{16} and R^{17} is independently hydrogen or (C_1-C_4) alkyl; R^{19} and R^{21} are taken together with the nitrogen to which they are attached to form a 3 to 8 membered heterocyclic ring.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $R^{22}-O-(C=O)-(NR^{21})$; each of R^{16} and R^{17} is independently hydrogen or (C_1-C_4) alkyl; R^{21} and R^{22} are taken together with the nitrogen or the oxygen to which they are attached to form a 3 to 8 membered heterocyclic ring.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1 to 4, preferably 1; R^{15} is selected from the group consisting of halo, -CN and R^{18} ; each of R^{16} and R^{17} is independently hydrogen or (C_1-C_4) alkyl; said R^{18} is selected from the group consisting of hydrogen, (C_1-C_4) alkyl, (C_6-C_{10}) aryl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl; wherein said (C_6-C_{10}) aryl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy, amino, (C_1-C_4) alkyl-NH-, $[(C_1-C_4)alkyl]_2-N$ - and (C_3-C_8) cycloalkyloxy; wherein said (C_3-C_8) cycloalkyl and (C_1-C_{10}) heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C_1-C_4) alkyl and $(C_1-C_4)alkyl-(C=O)-$.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1 to 4, preferably 1; R^{15} is selected from the group consisting of R^{18} ; each of R^{16} and R^{17} is

independently hydrogen or (C₁-C₄)alkyl; wherein said R¹⁸ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl.

In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p-; wherein p is 1 to 4, preferably 1; R¹⁵ is selected from the group consisting of (R¹⁹R²⁰)N-, (R¹⁹R²⁰)N-(C=O),
 5 (R¹⁹R²⁰)N-(SO₂); (R¹⁹R²⁰)N-(C=O)-(NR²¹)- and (R¹⁹R²⁰)N-(C=O)-O; each of R¹⁶ and R¹⁷ is independently hydrogen or (C₁-C₄)alkyl; and wherein R¹⁹ and R²⁰ are taken together with the nitrogen to which they are attached to form a 3 to 8-membered heterocyclic ring.

In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p-; wherein p is 1 to 4, preferably 1; R¹⁵ is selected from the group consisting of R¹⁹-(C=O)-(NR²¹)-, (R¹⁹R²⁰)N-(C=O)-
 10 (NR²¹), -NR¹⁹R²⁰, (R¹⁹R²⁰)N-(C=O)-(NR²¹)-; R²²(S=O)-; R²²(SO₂)-(NR²¹)-; R²²-O-(C=O)-(NR²¹)- and (R¹⁹R²⁰)N-(C=O)-O-; each of R¹⁶ and R¹⁷ is independently hydrogen or (C₁-C₄)alkyl; wherein each of R¹⁹, R²⁰ and R²¹ is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein the (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-
 15 C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by 1-3 substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy, wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-
 20 C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-; and wherein R²² is selected from the group consisting of (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein the (C₆-C₁₀)aryl, (C₃-
 25 C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by 1-3 substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also
 30 optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-.

In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p-; wherein p is 1 to 4, preferably 1; R¹⁵ is selected from the group consisting of R¹⁹-(C=O)-(NR²¹)-, R¹⁹-O-(C=O)-
 35 (NR²¹)- and (R¹⁹R²⁰)N-(C=O)-(NR²¹); each of R¹⁶ and R¹⁷ is independently hydrogen or (C₁-C₄)alkyl; wherein R¹⁹ and R²¹ are taken together with the nitrogen, the carbon or the oxygen to which they are attached to form a 3 to 8 membered heterocyclic ring.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 0; and G is oriented at a position other than alpha to the point of attachment of the Z ring to Y.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 0; and G is oriented at a position *meta* to the point of attachment of the Z ring to Y.

5 In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1 to 4, preferably 1; and G is oriented at a position other than alpha to the point of attachment of the Z ring to Y.

In another embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1 to 4, preferably 1; and G is oriented at a position *meta* to the point of attachment of the Z ring to Y.

10 In another preferred embodiment of the invention, one or two of R^1 , R^2 , R^3 , R^4 , R^{10} , R^{11} , R^{12} and R^{13} is a group other than hydrogen.

In a more preferred embodiment of the invention, each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} is hydrogen.

15 In another preferred embodiment of the invention, either X or Z is not substituted by any optional substituents.

In another preferred embodiment of the invention, both X and Z are not substituted by any optional substituents.

In another preferred embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 0; R^{15} is selected from the group consisting of halo, -CN and (C_1-C_{10}) heteroaryl. More preferably, 20 R^{15} is bromo, fluoro, -CN or oxadiazolyl, preferably [1,3,4] oxadiazol-2-yl.

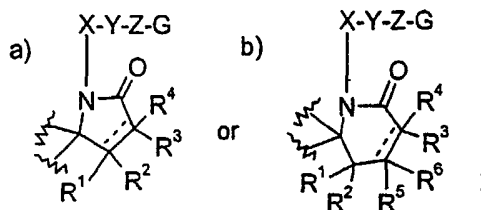
In another preferred embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 0 or 1; R^{15} is R^{18} ; each of R^{16} and R^{17} is hydrogen; and R^{18} is independently hydrogen or (C_1-C_4) alkyl; preferably methyl.

25 In another preferred embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 0 or 1; wherein G is oriented at a position *para* to the point of attachment of the Z ring to Y.

In another preferred embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is $R^{19}-(C=O)-(NR^{21})$; each of R^{16} or R^{17} is independently hydrogen; R^{19} is (C_1-C_4) alkyl, more preferably methyl, ethyl, or butyl; or (C_3-C_8) cycloalkyl, more preferably cyclobutyl; and R^{21} is hydrogen.

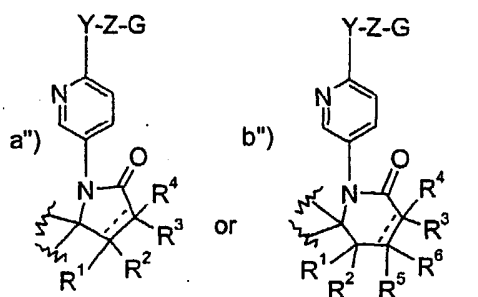
30 In another preferred embodiment of the invention, G is $R^{15}-(CR^{16}R^{17})_p$; wherein p is 1; R^{15} is (C_1-C_{10}) heteroaryl, such as 2-pyrazolyl; and wherein each of R^{16} and R^{17} is independently hydrogen.

In another preferred embodiment of the invention, the heterocyclic ring "A" has the formula a) or b):



wherein X is (C₁-C₁₀)heteroaryl selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl; and Y is selected from the group consisting of a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- and -CH₂O-; more preferably Y is oxygen, -OCH₂- or -CH₂O-; most preferably Y is oxygen.

- 5 Other preferred compounds of the invention include compounds of formula I, wherein the heterocyclic ring "A" has the formula a) or b), as defined above; X is (C₁-C₁₀)heteroaryl selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably X is pyridinyl; most preferably wherein the pyridinyl together with the "A" ring and the group Y-Z-G has the formula:



10

wherein Y is a bond, oxygen, sulfur, -CH₂-, >SO₂-, -OCH₂- or -CH₂O-; preferably Y is oxygen, -OCH₂- or -CH₂O-; more preferably Y is oxygen.

- Other preferred compounds of the invention include compounds of formula I, wherein the heterocyclic ring "A" has the formula a) or b), as defined above; X is pyridinyl, most preferably wherein the pyridinyl together with the "A" ring and the group Y-Z-G has the formula a) or b) as defined above; Y is oxygen; Z is (C₆-C₁₀)aryl, preferably phenyl; G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 1; R¹⁵ is (C₁-C₁₀)heteroaryl, such as 2-pyrazolyl; each of R¹⁶ and R¹⁷ is independently hydrogen or (C₁-C₄)alkyl, such as methyl, preferably hydrogen; and wherein G is oriented at a position *para* to the point of attachment of the Z ring to Y.

- 20 Most preferred compounds of the invention include compounds of formula I, wherein the heterocyclic ring "A" has the formula a) or b), as defined above; X is pyridinyl, most preferably wherein the pyridinyl together with the "A" ring and the group Y-Z-G has the formula a) or b) as defined above; Y is oxygen; Z is (C₆-C₁₀)aryl, preferably phenyl; G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 0; R¹⁵ is selected from the group consisting of hydrogen, -CN, halo and oxadiazolyl; and wherein G is oriented at a position *para* to the point of attachment of the Z ring to Y.

- Other most preferred compounds of the invention include compounds of formula I, wherein the heterocyclic ring "A" has the formula a) or b), as defined above; X is pyridinyl, most preferably wherein the pyridinyl together with the "A" ring and the group Y-Z-G has the formula a) or b) as defined above; Y is oxygen; Z is (C₆-C₁₀)aryl, preferably phenyl; G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein p is 1; R¹⁵ is R¹⁹-(C=O)-(NR²¹)-; each of R¹⁶ and R¹⁷ is independently

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hydrogen; R¹⁹ is selected from the group consisting of (C₁-C₄)alkyl and (C₃-C₈)cycloalkyl, such as methyl, ethyl, propyl, butyl, or cyclobutyl; R²¹ is selected from the group consisting of hydrogen or (C₁-C₄)alkyl; and wherein G is oriented at a position *para* to the point of attachment of the Z ring to Y.

- 5 Other compounds of the invention are selected from the group consisting of:
- 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 10 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,3,8,10-tetraaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 4-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,1-dioxo-1λ⁶-thia-2,4,7,9-tetraaza-spiro[4.5]decane-3,6,8,10-tetraone;
- 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,4,6,8,10-pentaone;
- 15 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-2,2-dioxo-2λ⁶-thia-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
- 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-2,2-dioxo-2λ⁶-thia-1,8,10-triaza-spiro[5.5]undecane-7,9,11-trione;
- 20 1-[6-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
- 1-[6-(4-Cyclobutylmethoxymethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 1-[6-(4-(2-Oxo-pyrrolidin-1-ylmethyl)-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 25 1-[6-(1H-Indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-3-methyl-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 1-[6-(3-Fluoro-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 30 4-[5-(2,7,9,11-Tetraoxo-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- N-{4-[5-(2,7,9,11-Tetraoxo-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzyl}-
- 35 acetamide;
- Azetidine-1-carboxylic acid 4-[5-(2,7,9,11-tetraoxo-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzylamide;

- 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 5 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 10 4-[5-(2,6,8,10-Tetraoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- N-{4-[5-(2,6,8,10-Tetraoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- Azetidine-1-carboxylic acid 4-[5-(2,6,8,10-tetraoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzylamide;
- 15 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,6,8,10-tetraone;
- 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,3,8,10-tetraaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,3,8,10-tetraaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 20 4-[5-(2,7,9,11-Tetraoxo-1,3,8,10-tetraaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- N-{4-[5-(2,7,9,11-Tetraoxo-1,3,8,10-tetraaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- 25 Azetidine-1-carboxylic acid 4-[5-(2,7,9,11-tetraoxo-1,3,8,10-tetraaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzylamide;
- 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,3,8,10-tetraaza-spiro[5.5]undecane-2,7,9,11-tetraone;
- 4-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,1-dioxo-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]decane-3,6,8,10-tetraone;
- 30 4-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,1-dioxo-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]decane-3,6,8,10-tetraone;
- 4-[5-(1,1,3,6,8,10-Hexaoxo-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]dec-4-yl)-pyridin-2-yloxy]-benzonitrile;
- 35 N-{4-[5-(1,1,3,6,8,10-Hexaoxo-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]dec-4-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- Azetidine-1-carboxylic acid 4-[5-(1,1,3,6,8,10-hexaoxo-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]dec-4-yl)-pyridin-2-yloxy]-benzylamide;

- 1,1-Dioxo-4-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1 λ^6 -thia-2,4,7,9-tetraaza-spiro[4.5]decane-3,6,8,10-tetraone;
- 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,4,6,8,10-pentaone;
- 5 4-[5-(2,4,6,8,10-Pentaoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- N-{4-[5-(2,4,6,8,10-Pentaoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- Azetidine-1-carboxylic acid 4-[5-(2,4,6,8,10-pentaoxo-1,3,7,9-tetraaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzylamide;
- 10 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,4,6,8,10-pentaone;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,3,7,9-tetraaza-spiro[4.5]decane-2,4,6,8,10-pentaone;
- 15 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-2,2-dioxo-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-2,2-dioxo-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
- 4-[5-(2,2,6,8,10-Pentaoxo-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- 20 N-{4-[5-(2,2,6,8,10-Pentaoxo-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- Azetidine-1-carboxylic acid 4-[5-(2,2,6,8,10-pentaoxo-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzylamide;
- 25 2,2-Dioxo-1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-2 λ^6 -thia-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
- 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-2,2-dioxo-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undecane-7,9,11-trione;
- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-2,2-dioxo-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undecane-7,9,11-trione;
- 30 4-[5-(2,2,7,9,11-Pentaoxo-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzonitrile;
- N-{4-[5-(2,2,7,9,11-Pentaoxo-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzyl}-acetamide;
- 35 Azetidine-1-carboxylic acid 4-[5-(2,2,7,9,11-pentaoxo-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undec-1-yl)-pyridin-2-yloxy]-benzylamide;
- 2,2-Dioxo-1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-2 λ^6 -thia-1,8,10-triaza-spiro[5.5]undecane-7,9,11-trione;

- 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;
 4-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
 N-[4-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
 5 acetamide;
 Azetidine-1-carboxylic acid 4-[5-(6,8,10-trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-
 2-yloxy]-benzylamide;
 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-
 trione;
 10 1-[6-(3-Fluoro-4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-
 spiro[5.5]undecane-2,7,9,11-tetraone;
 1-[6-(2-Fluoro-4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-
 spiro[5.5]undecane-2,7,9,11-tetraone;
 1-[6-(3-Methyl-4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,8,10-triaza-
 15 spiro[5.5]undecane-2,7,9,11-tetraone;
 1-[4-(4-[1,3,4]Oxadiazol-2-yl-phenoxy)-phenyl]-1,8,10-triaza-spiro[5.5]undecane-
 2,7,9,11-tetraone;
 1-[6-(Pyridin-4-yloxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
 1-[5-(Pyridin-4-yloxy)-pyridin-2-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
 20 1-[4-(Pyridin-4-yloxy)-phenyl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-tetraone;
 1-[4-(Pyridin-4-yloxy)-phenyl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
 Azetidine-1-carboxylic acid 4-[5-(2,6,8,10-tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-
 pyridin-2-yloxy]-benzylamide; and
 the pharmaceutically acceptable salts thereof.
 25 Specific preferred compounds of formula I are selected from the group consisting of:
 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
 1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-
 tetraone;
 4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
 30 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-
 2,6,8,10-tetraone;
 1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
 N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
 acetamide;
 35 N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
 propionamide;
 N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
 butyramide;

Pentanoic acid 4-[5-(2,6,8,10-tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzylamide;

Cyclobutanecarboxylic acid 4-[5-(2,6,8,10-tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzylamide;

- 5 1-[6-(4-Bromo-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;

and the pharmaceutically acceptable salts thereof.

- The present invention also relates to a pharmaceutical composition for the treatment of
10 a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other diseases characterized by metalloproteinase activity in a
15 mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

- The present invention also relates to a pharmaceutical composition for the inhibition of matrix metalloproteinases or other metalloproteinases involved in matrix degradation, in a
20 mammal, including a human, comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

- The present invention also relates to a method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other
25 diseases characterized by matrix metalloproteinase activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

- 30 The present invention also relates to a method for the inhibition of matrix metalloproteinases or other metalloproteinases involved in matrix degradation, in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

- 35 The present inventors have also discovered that it is possible to identify inhibitors of formula I with differential metalloprotease activity (preferably MMP-13 inhibitory activity). One group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1. The compounds of the invention

also possess selectivity over a related group of enzymes known as reprolysins, such as TACE and aggrecanase. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and MMP-14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and 12. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 12 and 14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 2, 3, 7, 9 and 14. Most preferred compounds of the invention selectively inhibit MMP-13 preferentially over MMP-1, 2, 3, 7, 9, 12 and 14 and mammalian reprolysins.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

"Connective tissue disorders" as used herein refers to disorders such as degenerative cartilage loss following traumatic joint injury, osteoarthritis, osteoporosis, Paget's disease, loosening of artificial joint implants, periodontal disease and gingivitis.

"Destruction of articular cartilage" as used herein refers to connective tissue disorders resulting in articular cartilage destruction, preferably joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, or juvenile rheumatoid arthritis, more preferably osteoarthritis.

"Inflammatory disorders" as used herein refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease and cachexia.

"Immunology/allergy disorders" as used herein refers to disorders such as organ transplant toxicity, allergic reactions, allergic contact hypersensitivity, autoimmune disorders such as those disorders associated with granulomatous inflammation/tissue remodeling (such as asthma), immunosuppression and sarcoid.

"Infectious diseases," including those mediated by viruses, bacteria, fungi or mycobacterial infection, as used herein refers to disorders such as septic arthritis, AIDS, fever; Prion diseases, myasthenia gravis, Malaria, sepsis, hemodynamic shock and septic shock.

"Respiratory diseases" as used herein refers to disorders such as chronic obstructive pulmonary disease (including emphysema), acute respiratory distress syndrome, asthma, hyperoxic alveolar injury and idiopathic pulmonary fibrosis and other fibrotic lung diseases.

5 "Cardiovascular diseases" as used herein refers to disorders such as atherosclerosis including atherosclerotic plaque rupture; aortic aneurysm including abdominal aortic aneurysm and brain aortic aneurysm; congestive heart failure; myocardial and cerebral infarction; stroke; cerebral ischemia; coagulation and acute phase response; left ventricular dilation; post ischemic reperfusion injury; angiofibromas; hemangiomas; and restenosis.

10 "Eye diseases" as used herein refers to disorders such as aberrant angiogenesis, ocular angiogenesis, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, macular degeneration (including "Age Related Macular Degeneration (ARMD) including both wet and dry forms), proliferative vitreoretinopathy and retinopathy of prematurity.

"Metabolic diseases" as used herein refers to disorders such as diabetes (including non-insulin dependent diabetes mellitus, diabetic retinopathy, insulin resistance, diabetic ulceration).

15 "Central Nervous System" (CNS) disorders as used herein refers to disorders such as head trauma, spinal cord injury, inflammatory diseases of the central nervous system, neuro-degenerative disorders (acute and chronic), Alzheimer's disease, demyelinating diseases of the nervous system, Huntington's disease, Parkinson's disease, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, migraine, depression and anorexia.

20 "Liver/Kidney diseases" as used herein refers to disorders such as nephrotic syndromes such as glomerulonephritis and glomerular disease of the kidney, proteinuria, cirrhosis of the liver and interstitial nephritis.

25 "Reproductive Health disorders" as used herein refers to disorders such as endometriosis, contraception (male/female), dysmenorrhea, dysfunctional uterine bleeding, premature rupture of fetal membranes and abortifacant.

"Gastric disorders" as used herein refers to disorders such as colonic anastomosis and gastric ulcers.

30 "Skin disorders" as used herein refers to disorders such as skin aging, pressure sores, psoriasis, eczema, dermatitis, radiation damage, tissue ulceration, decubital ulcers, epidermolysis bullosa, abnormal wound healing (topical and oral formulations), burns and scleritis.

35 "Cancers" as used herein refers to disorders such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer, tumor invasion, tumor growth tumor metastasis, cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and biliary passages, pancreas, larynx, lung, bone, connective tissue, skin, cervix uteri, corpus endometrium, ovary, testis, bladder, kidney and other urinary tissues, eye brain and central nervous system, thyroid

and other endocrine gland, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies including leukemias and lymphomas including lymphocytic, granulocytic and monocytic.

5 The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the
10 aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-
15 labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

This invention also encompasses pharmaceutical compositions containing prodrugs of
25 compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprotolysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy, sulfonamide or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amido, amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine
35 sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl

esters, which are covalently, bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include dimers of compounds of formula I.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies (such as infliximab, D2E7 and CDP-870) and TNF receptor immunoglobulin molecules (such as etanercept), ICE inhibitors, MEKK1 inhibitors, COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib and etoricoxib; low dose methotrexate, lefunimide, steroids, glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release inhibitors, IL-1 receptor antagonists such as Kineret®, CCR-1 antagonists, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, paracoxib, etoricoxib and rofecoxib, analgesics, steroids, glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release inhibitors, CCR-1 antagonists, LTD-4, LTB-4 and 5-LO inhibitors, p38 kinase inhibitors and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, paclitaxel, docetaxel and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers (such as amlodipine and nifedipine), lipid lowering agents such as statins (such as lovastatin, atorvastatin, pravastatin and simvastatin), adrenergics such as doxazosin and terazosin; fibrates, beta-blockers, ACE inhibitors (such as captopril, lisinopril, fosinopril, enalapril and quinapril), Angiotensin-2 receptor antagonists such as losartan and irbesartan; nitrates, CCB's, diuretics such as digitalis and platelet aggregation inhibitors. The compounds of the present invention may also

be used in combination with plaque rupture preventive agents such as statins, zithromax, NSAIDs including aspirin, heparin, urarfarin, abciximab, TPA and platelet Inhibitors. The compounds of the present invention may also be used in combination with stroke treatment agents such as NIF, NHEI's and CCRIR antagonists.

5 The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, carbadopa, L-dopa, dopamine receptor agonists such as ropinirole, pergolide and pramipexole; MAOB inhibitors such as selegiline and rasagiline, catechol-O-methyltransferase inhibitors such as tolcapone, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, 10 Nicotine agonists, NK-1 inhibitors, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

 The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and 15 immunosuppressant agents such as FK-506 and rapamycin.

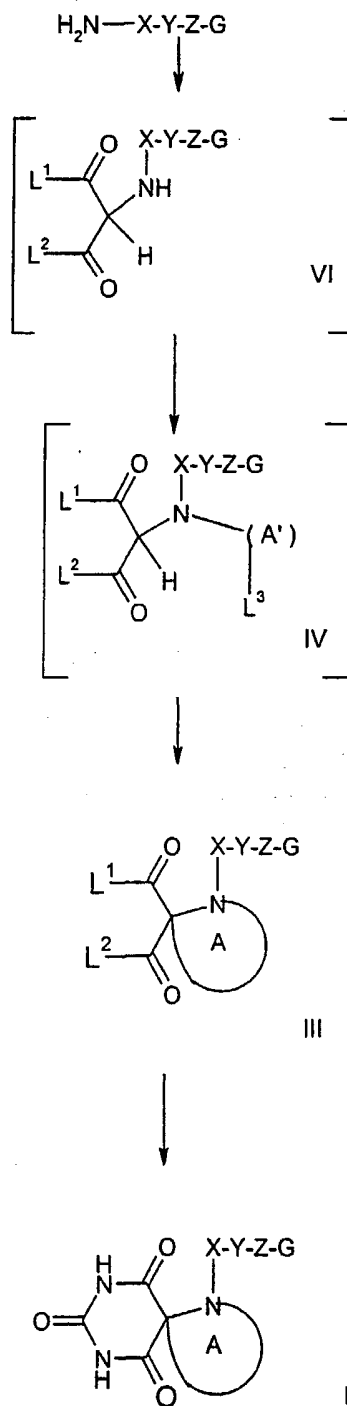
 The compounds of the present invention may also be used in combination with agents for the treatment of respiratory diseases such as PDE-IV inhibitors, steroidal such as fluticasone, triamcinolone, budesonide, budesonide and beclomethasone, anticholinergics such as ipratropium, sympathomimetics such as salmeterol, albuterol and Xopenex, 20 decongestants such as fexofenadine, loratadine and cetirizine; leukotriene antagonists such as zafirlukast and motelukast; and mast cell stabilizers such as zileuton.

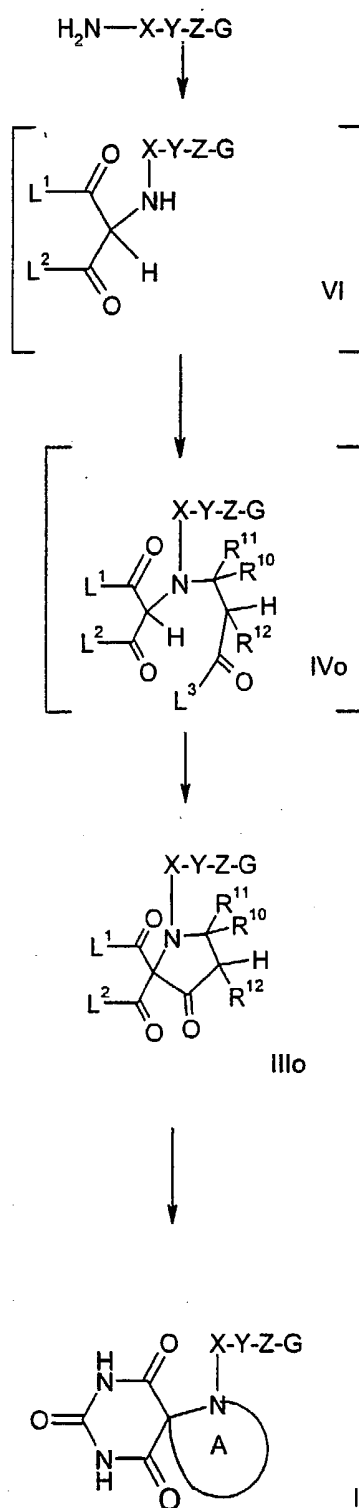
 The compounds of the present invention may also be used in combination with agents for the treatment of skin disorders such as tretinoin, isotretinoin, steroids such as cortisone and mometasone, antibiotics such as tetracycline, antifungals such as clotrimazole, 25 miconazole and fluconazole and PDE-IV inhibitors.

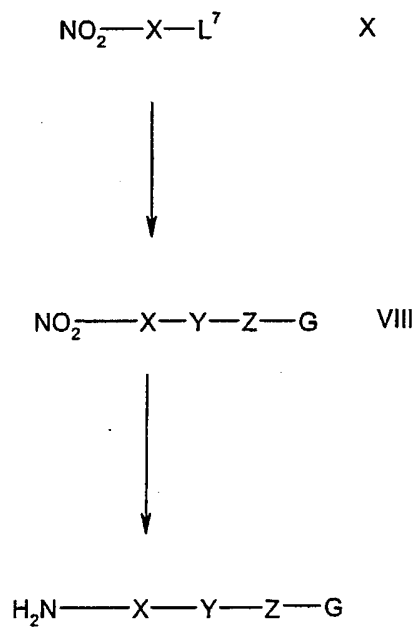
 The compounds of the present invention may also be used in combination with agents for the treatment of diabetes such as insulin, including human or humanized insulin and inhaled insulin, aldose reductase inhibitors, sorbitol dehydrogenase inhibitors, antidiabetic agents such as biguanides such as metformin; glitazones, glycosidase inhibitors such as 30 acarbose, sulfonylureas such as glimepiride and glipizide; and thiazolidinediones such as pioglitazone, rosiglitazone and troglitazone. Preferred combinations are useful for treating the side effects of diabetes such as retinopathy, nephropathy and neuropathy, preferably retinopathy.

Detailed Description of the Invention

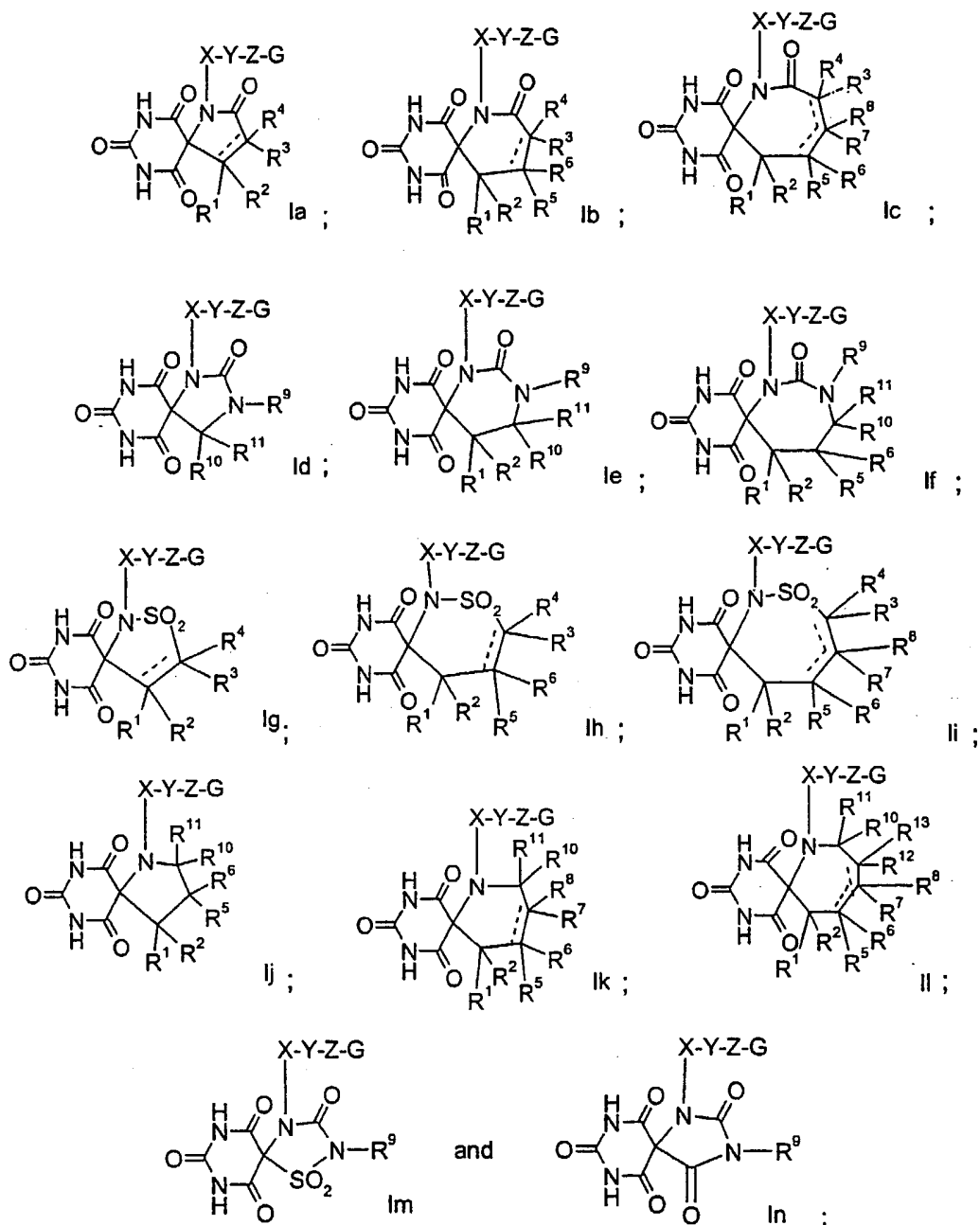
35 The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated each of X, Y, Z, G, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹ and R²² in the reaction Schemes and the discussion that follows is defined as above.

SCHEME 1

SCHEME 2

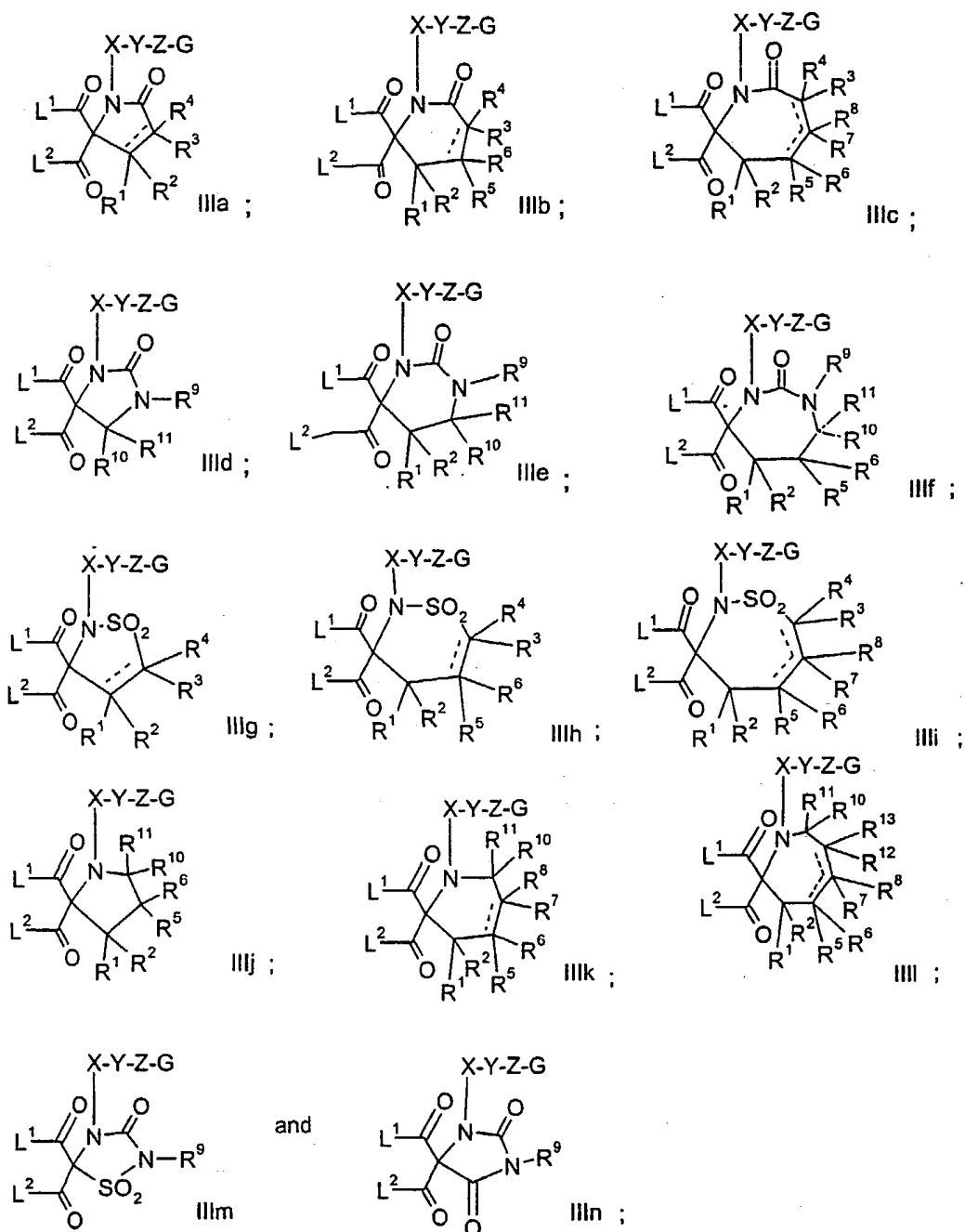
SCHEME 3

Scheme 1 refers to the preparation of compounds of the formula I. Referring to Scheme 1, compounds of formula I, wherein the heterocyclic ring "A" has the formulae a-n (i.e., a compound of the formulae Ia-In, respectively):



5

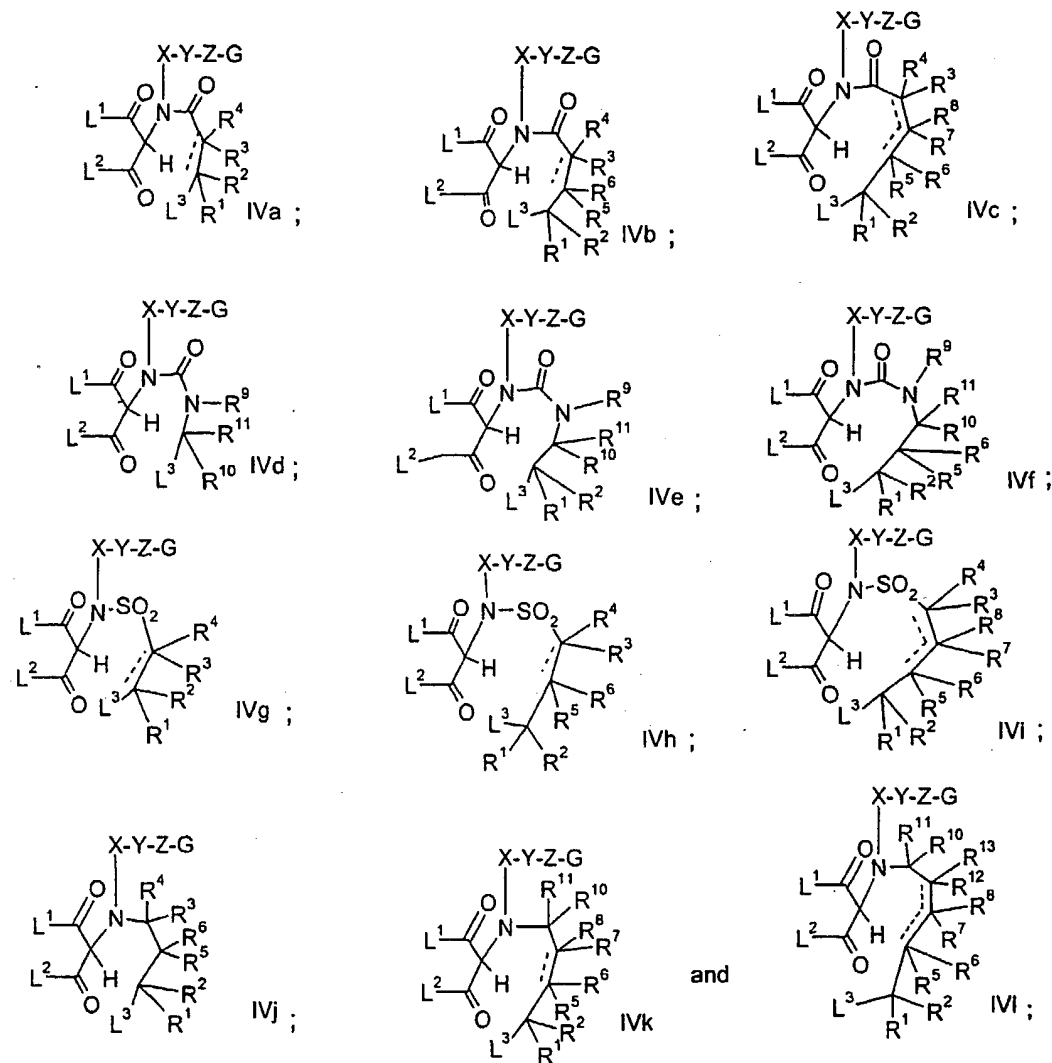
can be prepared by reacting a compound of the formulae IIIa-IIIIn, respectively:



- wherein L^1 and L^2 are leaving groups such as alkoxy, preferably methoxy, ethoxy or benzyloxy, more preferably methoxy or ethoxy, with a urea of formula II (i.e., $H_2N-(CO)-NH_2$) in the presence of a suitable base in a polar solvent. Suitable bases include alkoxide bases, such as sodium methoxide, sodium ethoxide, or potassium *tert*-butoxide, preferably sodium ethoxide. Suitable solvents include tetrahydrofuran, dimethylformamide, or alcohols (such as ethanol), preferably tetrahydrofuran or dimethylformamide. The aforesaid reaction is conducted at a
- 5

temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 5 minutes to about 8 hours.

A compound of formulae IIIa-III, respectively, can be prepared by reacting a compound of formulae IVa-IVl, respectively:

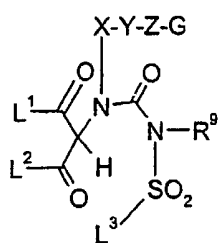


5

wherein L¹ and L² are leaving groups such as alkoxy, preferably methoxy, ethoxy or benzyloxy, more preferably methoxy or ethoxy and wherein L³ is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs), preferably halo, such as bromo or iodo, with a suitable base in a polar solvent. Suitable bases include tertiary amines, such as triethylamine. Other suitable bases include a strongly basic macro-reticular resin or gel type resin, such as Amberlyst 400[®] resin (hydroxide form). Suitable solvents include alcoholic solvents, preferably ethanol. The aforesaid reaction can be conducted at a temperature of about -10 °C to about 50 °C, preferably about 20 °C, for a period of about 6 to about 36 hours.

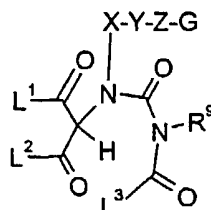
10

A compound of formulae IIIm-III n, respectively, can be prepared by reacting a compound of formulae IVm-IV n, respectively:



IVm

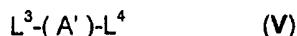
and



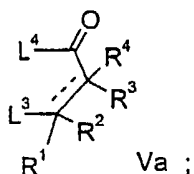
IVn

- wherein L^3 is a suitable leaving group, with a suitable base in a polar solvent according to methods analogous to the preparation of the compounds of formulae IIIa-IIIi in the foregoing paragraph. Suitable leaving groups of the formula L^3 include halo, *para*-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs). Preferably L^3 is halo, such as chloro. The aforesaid reaction can be conducted at a temperature of about 0°C to about 50°C, preferably about 20 °C, for a period of about 1 hour to about 4 hours. Suitable solvents include tetrahydrofuran, dimethylformamide and alcohol.

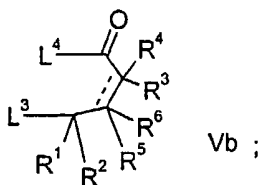
A compound of formulae IVa-IVi, respectively, can be prepared by reacting a compound of formula VI with a compound of general formula



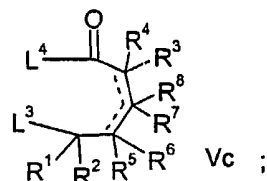
(i.e., a compound of formulae Va-Vi, respectively):



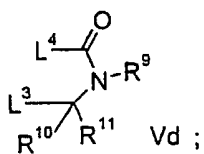
Va ;



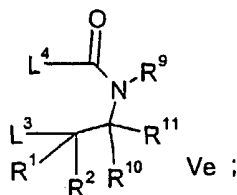
Vb ;



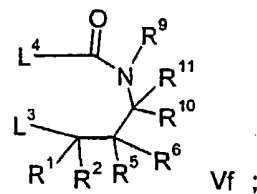
Vc ;



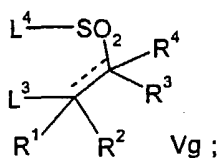
Vd ;



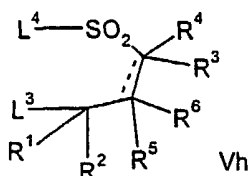
Ve ;



Vf ;

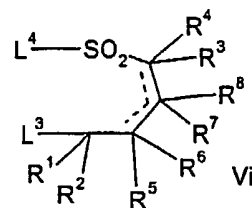


Vg ;



Vh

and



Vi

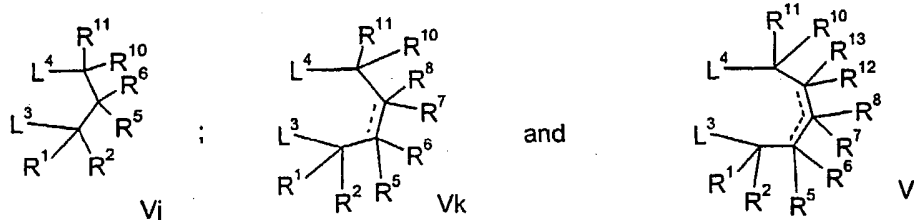
wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs). Preferably L^3 is halo, such as bromo, chloro or iodo. Preferably L^4 is chloro or fluoro. Optionally, the aforementioned reaction may be conducted in the presence of a tertiary amine base, such as *N,N*-dimethylaniline or pyridine, in the presence of a suitable solvent, such as a hydrocarbon solvent (benzene or toluene), tetrahydrofuran or methylene chloride. The aforementioned reaction is conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 30 minutes to about 6 hours.

Preferably, the aforementioned reaction is conducted in an aromatic hydrocarbon solvent, such as benzene or toluene, in the absence of the aforementioned base.

A compound of formulae IVj-IVl, respectively, can be prepared by reacting a compound of formula VI with a compound of formula:



(i.e., a compound of formulae Vj-Vl, respectively):

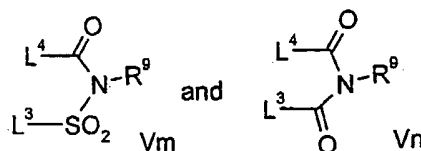


wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), according to the methods analogous to those described in the preparation of the compounds of formulae IVa-IVi in the foregoing paragraph. Preferably L^3 is chloro, bromo, or iodo. Preferably L^4 is chloro, bromo, or iodo. The aforesaid reaction can be conducted at a temperature of about 0°C to about 50°C, preferably about 20°C, for a time period of about 30 minutes to about 12 hours.

Compounds of formulae IVm-IVn, respectively, can be prepared by reacting a compound of formula VI with a compound of formula



(i.e., a compound of formulas Vm-Vn, respectively):



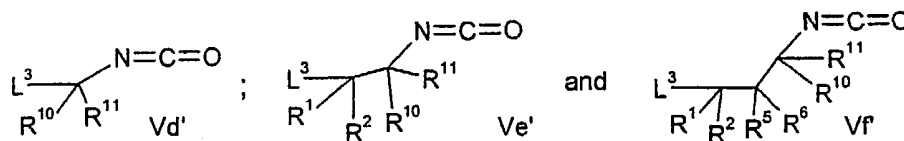
wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), according to the methods analogous to those described in the preparation of the compounds of formulae IVa-IVi in the foregoing paragraph. Preferably L^3 is

halo, such as chloro. Preferably L^4 is halo, such as chloro. The aforesaid reaction can be conducted at a temperature of about 0°C to about 80°C , preferably about 0°C to about 40°C , for a time period of about 30 minutes to about 8 hours.

Alternatively, compounds of formulae IVd, IVe and IVf, respectively, can be prepared by reacting a compound of formula VI with a compound of formula



(i.e., a compound of formulae Vd', Ve' and Vf', respectively):

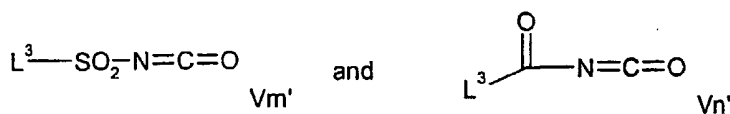


wherein L^3 is preferably halo, most preferably chloro, bromo, or iodo. Optionally, the
10 the aforementioned reaction can be conducted in the presence of a tertiary amine base in a suitable solvent. Suitable bases include *N,N*-dimethylaniline or pyridine. Suitable solvents include hydrocarbon solvent (benzene or toluene), tetrahydrofuran, or methylene chloride, preferably aromatic hydrocarbon solvent, such as benzene or toluene. The aforementioned reaction is conducted at a temperature of about 20°C to about 90°C , preferably about 50°C to
15 about 80°C , for a time period of about 30 minutes to about 6 hours. Preferably, the aforementioned reaction is conducted in the absence of any aforementioned base.

Alternatively, compounds of formulae IVm and IVn, respectively, can be prepared by reacting a compound of formula VI with a compound of formula

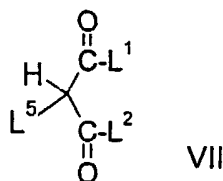


(i.e., a compound of formulae Vm' and Vn', respectively):



wherein L^3 is preferably halo, most preferably chloro. The aforementioned reaction can be conducted optionally in the presence of a tertiary amine base in a suitable solvent. Suitable
25 bases include *N,N*-dimethylaniline or pyridine. Suitable solvents include a hydrocarbon solvent (benzene or toluene), tetrahydrofuran or methylene chloride, preferably aromatic hydrocarbon solvent, such as benzene or toluene. The aforesaid reaction can be conducted at a temperature of about -10°C to about 50°C , preferably about 0°C to about 30°C , for a time period of about 30 minutes to about 12 hours. Preferably, the aforementioned reaction is conducted in the absence of any aforementioned base.

30 A compound of formula VI can be prepared by reacting a compound of formula $\text{H}_2\text{N}-\text{X}-\text{Y}-\text{Z}-\text{G}$ with a compound of the formula VII:



wherein L^1 and L^2 are leaving groups, such as methoxy, ethoxy, or benzyloxy; preferably ethoxy; and L^5 is a leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs); preferably halo; most preferably chloro or bromo. The aforesaid reaction can be performed either neat or in the presence of a suitable solvent, preferably neat, in the presence of a suitable base. Suitable solvents include tetrahydrofuran or dimethylformamide. Suitable bases include a weak tertiary amine base, preferably tertiary aniline bases, most preferably N,N-dimethylaniline. Preferably, the aforementioned reaction is conducted at a temperature of about 23°C to about 100°C, preferably about 50°C to about 90°C, for a time period of about 30 minutes to about 24 hours.

In the aforesaid reactions, each of the compounds of formulae IVj-IVl may be isolated, but are preferably carried on to the next step without isolation. Thus, in Scheme 1, the compound of formulae IIIj-IIIll is preferably prepared in a one pot preparation from a compound of the formula VI.

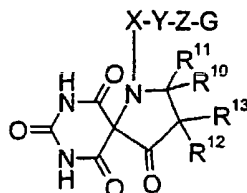
If the compounds of the formulae IVj-IVl are not isolated, the suitable solvent for the one-pot preparation is dimethylformamide, tetrahydrofuran, or alcohols, preferably alcohols, such as ethanol. Preferably, the one-pot preparation is conducted in the presence of an alkoxide base, preferably sodium methoxide or sodium ethoxide. The aforesaid one pot preparation is conducted at a temperature of about 40°C to about 90°C, preferably about 60°C to about 80°C, for a time period of about 15 minutes to about 12 hours.

The compounds of formula $H_2N-X-Y-Z-G$ are commercially available or can be made by methods well known to those skilled in the art. Alternatively, the compounds of formula $H_2N-X-Y-Z-G$ can be prepared as described in Scheme 3.

A compound of the formula VII can be made by methods well known in the art such as those described in PCT Patent Publication WO 98/58925 or reviewed in The Organic Chemistry of Drug Synthesis, D. Lednicher and L. A. Mitscher, Volume 1, pages 167 to 277 and references therein. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

Compounds of the formula II are commercially available or can be made by methods well known to those skilled in the art.

Scheme 2 refers to the preparation of a compound of the formula I, wherein the heterocyclic ring "A" has the formula o, i.e., a compound of formula Io. Referring to Scheme 2, a compound of formula Io:

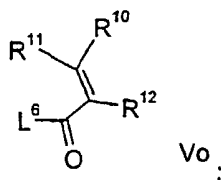


10;

can be prepared by reacting a compound of the formula IIIo, wherein L^1 and L^2 are leaving groups, with a urea of formula II (*i.e.*, $H_2N-(CO)-NH_2$) in the presence of a suitable base in a polar solvent. Suitable leaving groups include methoxy, ethoxy, or benzyloxy, preferably ethoxy. Suitable bases include alkoxide bases, such as sodium methoxide, sodium ethoxide and potassium *tert*-butoxide, preferably sodium ethoxide. Suitable solvents include tetrahydrofuran, dimethylformamide, or alcohols (such as ethanol), preferably tetrahydrofuran or dimethylformamide. The aforesaid reaction is conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 5 minutes to about 8 hours.

A compound of formula IIIo can be prepared by reacting a compound of formula IVo, wherein L^3 is a leaving group, with a suitable base in a polar solvent. Suitable leaving groups include alkoxy (such as methoxy, ethoxy, or benzyloxy) or halo; preferably methoxy or ethoxy. Suitable bases include alkoxide bases, preferably sodium methoxide or sodium ethoxide. Suitable solvents include alcohols, preferably ethanol. The aforesaid reaction can be conducted at a temperature of about 0 °C to about 90 °C, preferably of about 60 °C to about 90 °C, for a period of about 1 hour to about 36 hours.

A compound of formula IVo can be prepared by reacting a compound of formula VI with the compound of formula Vo:



Vo;

wherein L^6 is a suitable leaving group, in a suitable solvent. Suitable L^6 includes alkoxy or halo, such as chloro; preferably alkoxy; more preferably methoxy or ethoxy. Optionally, the aforesaid reaction may be conducted in the presence of a suitable tertiary amine base, such as triethylamine, *N,N*-dimethylaniline, or pyridine. Suitable solvents, include hydrocarbon solvents (benzene or toluene), tetrahydrofuran, or methylene chloride, preferably tetrahydrofuran. Preferably, the aforementioned reaction is conducted in tetrahydrofuran or dimethylformamide, in the presence of the aforementioned suitable tertiary amine base. The aforesaid reaction may be conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 30 minutes to about 6 hours.

In the aforesaid reactions, a compound of formula **IVo** may be isolated, but is preferably carried on to the next step without isolation. Thus, in Scheme 1, a compound of formula **IIIo** is preferably prepared in a one-pot preparation from a compound of the formula **VI**.

5 If the compounds of the formulae **IVo** are not isolated, the suitable solvent for the one-pot preparation is dimethylformamide, tetrahydrofuran, or alcohols, preferably alcohol, such as ethanol. The aforesaid one pot preparation is suitably conducted at a temperature of about 0°C to about 70°C, preferably about 23°C to about 60°C, for a time period of about 30 minutes to about 24 hours.

10 A compound of formula **VI** can be prepared by reacting a compound of formula $H_2N-X-Y-Z-G$ with a compound of the formula **VII** as described Scheme 1.

Scheme 3 refers to the preparation of compounds of the formula $H_2N-X-Y-Z-G$, which are intermediates useful in the preparation of compounds of formula **I** in Schemes 1 and 2. Referring to Scheme 3, compounds of formula $H_2N-X-Y-Z-G$ can be prepared by reacting a
15 compound of formula **VIII** with a reducing agent, such as tin II chloride, in the presence of a suitable acid, such as hydrochloric acid, in a polar protic solvent. Suitable solvents include an alcoholic solvent, water, or mixtures thereof, preferably a mixture of ethanol and water. The aforesaid reaction can be conducted at a temperature of about 40°C to about 100°C for a period of about 1 to about 12 hours.

20 Alternatively, the compounds of formula $H_2N-X-Y-Z-G$ can be prepared by reacting a compound of formula **VIII** with hydrogen gas, at a pressure between atmospheric pressure and 50 psi, in the presence of a catalyst and a polar solvent. Suitable catalysts include a palladium or platinum catalyst, preferably Adams catalyst (*i.e.*, platinum oxide), or palladium adsorbed on charcoal. Suitable solvents include an alcoholic solvent, preferably methanol.
25 The aforesaid reaction can be conducted at a temperature of about 20°C to about 50°C, preferably about 23°C, for a period of about 30 minutes to about 6 hours.

A compound of the formula **VIII**, wherein Y is oxygen, sulfur, $-CH_2S-$, $-CH_2O-$, $>NR^{14}$, $-CH_2[N(R^{14})]-$ or $-SO_2[N(R^{14})]-$, can be prepared by reacting a compound of formula **X**, wherein the group L^7 is fluoro or chloro, with a compound of the formula:

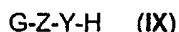
30 $G-Z-Y-H$ (IX)

wherein Y is oxygen, sulfur, $-CH_2S-$, $-CH_2O-$, $>NR^{14}$, $-CH_2[N(R^{14})]-$ or $-SO_2[N(R^{14})]-$, in the presence of a base in a polar aprotic solvent. Suitable bases include an alkali metal hydride base; preferably sodium hydride. Suitable solvents include dimethylformamide, tetrahydrofuran or 1,2-dimethoxyethane; preferably dimethylformamide. The aforesaid
35 reaction can be conducted at a temperature of about 40°C to about 140°C, preferably about 80°C to about 120°C, for about 1 hour to about 24 hours.

Alternatively, the aforesaid compound of formula **VIII**, wherein Y is oxygen, sulfur,

-CH₂S-, -CH₂O-, >NR¹⁴, -CH₂[N(R¹⁴)]- or -SO₂[N(R¹⁴)]-, can be prepared in presence of an alkali metal hydroxide base, preferably potassium hydroxide, optionally in the presence of a phase transfer catalyst, such as a quaternary ammonium or phosphonium salt, preferably tetrabutylammonium bromide, in an aromatic hydrocarbon solvent. Preferably the solvent is benzene or toluene. The aforesaid reaction can be conducted at a temperature of about 0°C to about 120°C, preferably at about 23°C, for about 1 hour to about 12 hours.

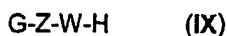
Alternatively, the aforesaid compound of formula VIII, wherein Y is oxygen, sulfur, -CH₂S-, -CH₂O-, >NR¹⁴, -CH₂[N(R¹⁴)]- or -SO₂[N(R¹⁴)]-, can be prepared under so called "Ulman coupling" conditions. Under such conditions, the aforesaid compound of formula VIII can be prepared by reacting a compound of formula X, wherein the group L⁷ is bromo or chloro, with a compound of the formula:



, wherein Y is oxygen, sulfur, -CH₂S-, -CH₂O-, >NR¹⁴, -CH₂[N(R¹⁴)]- or -SO₂[N(R¹⁴)]-, in the presence of a base and a catalyst in a polar aprotic solvent. Suitable bases include an alkali metal carbonate or hydroxide base, preferably potassium carbonate. Suitable catalysts include a copper (0) catalyst, preferably finely powdered copper bronze. Suitable solvents include dimethylformamide or 1-methyl-2-pyrrolidinone. The aforesaid reaction can be conducted at a temperature of about 80 °C to about 140 °C, for about 6 hours to about 24 hours.

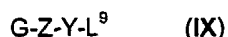
A compound of formula VIII, wherein the group Y is in an oxidized state, i.e., >SO₂, >S=O, -CH₂SO-, -CH₂SO₂-, SO(CH₂)_n- or -SO₂(CH₂)_n-, can be prepared by reacting a corresponding compound of formula VIII, wherein the group Y is in a corresponding lower oxidation state, with a suitable oxidizing agent in a solvent. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is >SO₂ and >S=O is a compound of formula VIII, wherein the group Y is S. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is -CH₂SO₂- and -CH₂SO- is a compound of formula VIII, wherein the group Y is -CH₂S-. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is -SO₂(CH₂)_n- and -SO(CH₂)_n- is a compound of formula VIII, wherein the group Y is -S-(CH₂)_n-. Suitable oxidizing agents include a peroxy acid, preferably peracetic acid, or an organic peroxide, preferably *m*-chloroperoxybenzoic acid or *tert*-butyl hydroperoxide. Suitable solvents include methylene chloride or alcohol, such as ethanol. The aforesaid reaction can be conducted at a temperature of about -10°C to about 30°C, for about 1 hour to about 8 hours.

A compound of the formula VIII, wherein Y is -O(CH₂)_n-, -S(CH₂)_n- or -NR¹⁴(CH₂)_n-, respectively, can be prepared by reacting a compound of the formula X, wherein the group L⁷ is L⁸-(CH₂)_n- and wherein the group L⁸ is halo, such as chloro, bromo, iodo, mesyloxy (MsO), or tosyloxy (TsO), with a compound of formula:



wherein the group W is oxygen, sulfur, or -NR¹⁴, respectively, in the presence of a base in a polar aprotic solvent. Suitable bases include an alkali metal carbonate base, preferably potassium carbonate or cesium carbonate. Suitable solvents include dimethylformamide or tetrahydrofuran. The aforesaid reaction can be conducted at a temperature of about 23°C to about 80°C, preferably about 20°C to about 50°C, for about 1 to about 24 hours.

A compound of the formula VIII, wherein Y is >C=O, -CH=CH- or -C≡C-, can be prepared by reacting a compound of formula X, wherein the group L⁷ is dihydroxyborane; zinc halide, such as zinc chloride; or trialkyl tin, such as tributyl tin, with a compound of the formula:



wherein Y is >C=O, -CH=CH- or -C≡C-; and wherein the group L⁹ is halo; preferably chloro, bromo or iodo; in the presence of a catalyst in a solvent. Suitable catalysts include a palladium or nickel catalyst, preferably tetrakis triphenyl phosphine palladium (0) (Pd(PPh₃)₄). Suitable solvents include toluene, tetrahydrofuran, dimethylformamide, or dimethylsulfoxide. The aforesaid reaction can be conducted at a temperature of about 23°C to about 110°C, for a period of about 1 hour to about 24 hours. Such reactions can be facilitated by the presence of a copper salt, such as cuprous iodide or cuprous bromide.

Alternatively, a compound of the formula VIII, wherein Y is -C≡C-, can be prepared by reacting a compound of formula X, wherein L⁷ is halo or triflate, preferably bromo or iodo, with a compound of the formula:



in the presence of a base, such as a trialkylamine base, preferably triethylamine and a palladium catalyst, preferably Pd(PPh₃)₄ in a solvent. Suitable solvents include tetrahydrofuran or dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 23°C to about 60°C for a period of about 1 to about 24 hours.

A compound of the formula VIII, wherein Y is -CH₂(CH₂)_n-, can be prepared by reacting the aforementioned compound of the formula VIII, wherein Y is -CH=CH- or -C≡C-, with hydrogen gas, at ambient pressure to about 50 psi, in the presence of a palladium catalyst in a solvent. Preferably the palladium catalyst is palladium adsorbed on charcoal. Suitable solvents include methanol or ethyl acetate. The aforesaid reaction can be conducted at a temperature of about 20°C to about 50°C, for about 1 hour to about 24 hours.

Compounds of the formulae X and IX (i.e., compounds of the formulae G-Z-Y-H, G-Z-W-H, or G-Z-Y-L⁹) are either commercially available or are well known and can be prepared by methods known to those skilled in the art.

The compounds of the formula I, which are basic in nature, are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a

pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a
5 substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition
10 salts, *i.e.*, salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical
15 bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations and then
20 evaporating the resulting solution to dryness, preferably under reduced pressure.

Alternatively, these salts may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction
25 and maximum product yields.

BIOLOGICAL ASSAYS

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reopolysins and, consequently, demonstrate their
35 effectiveness for treating diseases characterized by metalloproteinase activity is shown by the following *in vitro* and *in vivo* assay tests.

MMP Assays

MMP-13 selective inhibitors can be identified by screening the inhibitors of the present invention through the MMP fluorescence assays described below and selecting those agents with MMP-13/MMP-X inhibition IC_{50} ratios of 100 or greater and potency of less than 100 nM, where MMP-X refers to one or more other MMP's.

Non-selective collagenase inhibitors as used herein, unless otherwise mentioned, refer to agents which exhibit less than a 100 fold selectivity for the inhibition of MMP-13 enzyme activity over MMP-X enzyme activity or a potency of more than 100nM as defined by the IC_{50} results from the MMP-13/MMP-X fluorescence assays described below.

The ability of collagenase inhibitors to inhibit collagenase activity is well known in the art. The degree of inhibition of a particular MMP for several compounds has been well documented in the art and those skilled in the art will know how to normalize different assay results to those assays reported herein. The following assays may be used to identify matrix metalloproteinase inhibitors.

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μ g trypsin per 100 μ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM \longrightarrow 120 μ M \longrightarrow 12 μ M \longrightarrow 1.2 μ M \longrightarrow 0.12 μ M

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

Collagenase-1 is diluted to 240 ng/ml and 25 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 μ M in assay buffer. The assay is initiated by the addition of 50 μ l substrate per well of the microfluor plate to give a final concentration of 10 μ M.

Fluorescence readings (360 nm excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours

Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around

120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50} 's are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50} 's are reported to be less than 0.03 μ M then the inhibitors are assayed at concentrations of 0.3 μ M, 0.03 μ M and 0.003 μ M.

Inhibition of Gelatinase (MMP-2)

Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM $CaCl_2$, 20 μ M $ZnCl_2$ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \rightarrow 120 μ M \rightarrow 12 μ M \rightarrow 1.2 μ M \rightarrow 0.12 μ M

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \rightarrow 3 μ M \rightarrow 0.3 μ M \rightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration

versus percent of enzyme control. IC_{50} 's are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Stromelysin Activity (MMP-3)

Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours
5 with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM $CaCl_2$ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

10 10 mM → 120 μ M → 12 μ M → 1.2 μ M → 0.12 μ M

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further
15 1:4 dilution (i.e. 30 μ M → 3 μ M → 0.3 μ M → 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL
20 (0.875 nM).

A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)- NH_2) is diluted in assay buffer to 6 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 3 μ M substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and
25 subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the
30 data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50} 's are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Human 92 kD Gelatinase (MMP-9)

35 Inhibition of 92 kD gelatinase (MMP-9) activity is assayed using the Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg- NH_2 substrate (10 μ M) under similar conditions as described above for the inhibition of human collagenase (MMP-1).

Human recombinant 92 kD gelatinase (MMP-9, gelatinase B) is activated for 2 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37 C.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay
5 buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μM ZnCl₂, 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM → 120 μM → 12 μM → 1.2 μM → 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of
four inhibitor concentrations for each compound are performed in each assay. 25 μL of each
10 concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM → 3 μM → 0.3 μM → 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

15 Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.27 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μM. The assay is initiated by addition of 50 μL of
20 diluted substrate yielding a final assay concentration of 10 μM substrate. A 0 time fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time.
25 An early time point on the linear part of this curve is chosen for IC₅₀ determinations. The 0 time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that
30 gives a signal that is 50% of the positive enzyme control.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5 mM calcium chloride, 20 μM zinc chloride, 0.02% brij). Twenty-five
35 microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μ M, 3 μ M, 0.3 μ M and 0.03 μ M.

- 5 Substrate (Dnp-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ l is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nm excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

- 10 Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 μ M, inhibitors are then assayed at final concentrations of 0.3 μ M, 0.03 μ M, 0.003 μ M and 0.0003 μ M.

Collagen film MMP-13 Assay

- 15 Rat type I collagen is radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, Anal. Biochem., 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, Anal. Biochem., 104, 175-181 (1980)). When a solution containing collagenase is added to the well, the enzyme cleaves the insoluble collagen which unwinds and is thus solubilized. Collagenase activity is directly proportional to
20 the amount of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors are, therefore, compounds which reduce the radioactive counts released with respect to the controls with no inhibitor present. One specific embodiment of this assay is described in detail below.

- 25 For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure is used. Recombinant human proMMP-13 or proMMP-1 is activated according to the procedures outlined above. The activated MMP-13 or MMP-1 is diluted to 0.6 μ g/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂ , 1 μ M ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

- 30 Stock solutions of test compound (10mM) in dimethylsulfoxide are prepared. Dilutions of the test compounds in the Tris buffer, above, are made to 0.2, 2.0, 20, 200, 2000 and 20000 nM.

- 35 100 μ l of appropriate drug dilution and 100 μ l of diluted enzyme are pipetted into wells of a 96 well plate containing collagen films labeled with ¹⁴C-collagen. The final enzyme concentration is 0.3 μ g/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control is analyzed in triplicate. Triplicate controls are also run

for the conditions in which no enzyme is present and for enzyme in the absence of any compound.

The plates are incubated at 37°C for a time period such that around 30 - 50% of the available collagen is solubilized - determined by counting additional control wells at various time points. In most cases around 9 hours of incubation are required. When the assay has progressed sufficiently, the supernatant from each well is removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no enzyme) are subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor. The triplicate values for each point are averaged and the data graphed as percent release versus drug concentration. IC₅₀'s are determined from the point at which 50% inhibition of release of radiolabeled collagen is obtained.

To determine the identity of the active collagenases in cartilage conditioned medium, assays were conducted using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying selectivity. The cartilage conditioned medium was collected during the time at which collagen degradation was occurring and thus is representative of the collagenases responsible for the collagen breakdown. Assays were conducted as outlined above except that instead of using recombinant MMP-13 or recombinant MMP-1, cartilage conditioned medium was the enzyme source.

IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage

This assay uses bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily type II collagen and aggrecan. The tissue is used because it: (1) is very similar to articular cartilage, (2) is readily available, (3) is relatively homogeneous and (4) degrades with predictable kinetics after IL-1 stimulation.

Two variations of this assay have been used to assay compounds. Both variations give similar data. The two variations are described below:

Variation 1

Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) are placed into each well of a 24 well tissue culture plate. One ml of serumless medium is then added to each well. Compounds are prepared as 10 mM stock solutions in DMSO and then diluted appropriately in serumless medium to final concentrations, e.g., 50, 500 and 5000 nM. Each concentration is assayed in triplicate.

Human recombinant IL-1 α (5ng/mL) (IL-1) is added to triplicate control wells and to each well containing drug. Triplicate control wells are also set up in which neither drug nor IL-1 are added. The medium is removed and fresh medium containing IL-1 and the appropriate

drug concentrations is added on days 6, 12, 18 and 24 or every 3 - 4 days if necessary. The media removed at each time point is stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells has almost completely resorbed (about day 21), the experiment is terminated. The medium, is removed and stored. Aliquots (100 µl) from each well at each
5 time point are pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot.

Variation 2

10 The experimental set-up is the same as outlined above in Variation 1, until day 12. On day 12, the conditioned medium from each well is removed and frozen. Then one ml of phosphate buffered saline (PBS) containing 0.5 µg/ml trypsin is added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution is removed. Aliquots (50 µl) of the PBS/trypsin solution and the previous two
15 time points (days 6 and 12) are pooled, hydrolyzed and hydroxyproline content determined. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot. In this variation, the time course of the experiment is shortened considerably. The addition of
20 trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that has been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment produces only low background levels of collagen degradation in the cartilage explants.

Inhibition of TNF Production

25 The ability or inability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF is shown by the following in vitro assay:

Human Monocyte Assay

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times
30 in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180 µl of the cell suspension was aliquoted into flat bottom 96 well plates (Costar).
35 Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 µl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified

CO₂ incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF α using the R&D ELISA Kit.

Aggrecanase Assay

Primary porcine chondrocytes from articular joint cartilage are isolated by sequential
5 trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2×10^5 cells per well into 48 well plates with 5 μ Ci / ml ³⁵S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO₂.

The night before initiating the assay, chondrocyte monolayers are washed two times
10 in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.

Media and dilutions can be made as described in the Table below.

Control Media	DMEM alone (control media)
IL-1 Media	DMEM + IL-1 (5 ng/ml)
Drug Dilutions	<p>Make all compounds stocks at 10 mM in DMSO.</p> <p>Make a 100 μM stock of each compound in DMEM in 96 well plate. Store in freezer overnight.</p> <p>The next day perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM and 50 nM.</p> <p>Aspirate final wash from wells and add 50 μl of compound from above dilutions to 450 μl of IL-1 media in appropriate wells of the 48 well plates.</p> <p>Final compound concentrations equal 500 nM, 50 nM and 5 nM.</p> <p>All samples completed in triplicate with Control and IL-1 alone samples on each plate.</p>

15 Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to monitor ³⁵S-proteoglycan release. Control and IL-1 media are added to wells (450 μ l) followed by compound (50 μ l) so as to initiate the assay. Plates are incubated at 37°C, with a 5% CO₂ atmosphere.

20 At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μ l of papain

digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added and samples counted (LSC).

- 5 The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

10 The compounds of the present invention that were tested all have IC_{50} 's in at least one of the above assays of less than 100 μ M preferably less than 100nM. Certain preferred groups of compounds possess differential selectivity toward the various MMP's or ADAMs. One group of preferred compounds possesses selective activity towards MMP-13 over MMP-1. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-3 and MMP-7. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-3, MMP-7 and MMP-17. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-14. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-12 and MMP-14.

20 For administration to mammals, including humans, for the inhibition of matrix metalloproteinases, a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the compounds of the invention (hereinafter also known as the active compounds) will be administered at dosages of about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

30 The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

35 For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

For topical ocular administration, direct application to the affected eye may be employed in the form of a formulation as eyedrops, aerosol, gels or ointments, or can be incorporated into collagen (such as poly-2-hydroxyethylmethacrylate and co-polymers thereof), or a hydrophilic

polymer shield. The materials can also be applied as a contact lens or via a local reservoir or as a subconjunctival formulation.

For intraorbital administration a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in an aqueous solution or suspension (particle size less than 10 micron) may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH between 5 and 8, if necessary and the liquid diluent first rendered isotonic. Small amounts of polymers can be added to increase viscosity or for sustained release (such as cellulosic polymers, Dextran, polyethylene glycol, or alginic acid). These solutions are suitable for intraorbital injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intraorbitally at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

As with the other routes of administration and corresponding dosage forms described herein, dosage forms intended for oral administration are also suitably formulated to provide controlled-, sustained- and/or delayed release of the active ingredient. Typically, these would include delayed-release oral tablets, capsules and multiparticulates, as well as enteric-coated tablets and capsules which prevent release and adsorption of the active ingredient in the stomach of the patient and facilitate enteric delivery distal to the stomach, *i.e.*, in the intestine. Other typical oral dosage forms would include sustained-release oral tablets, capsules and multiparticulates which provide systemic delivery of the active ingredient in a controlled manner over a prolonged period of time, *e.g.*, a 24-hour period. Where rapid delivery of the active ingredient is required or desirable, a controlled-release oral dosage form may be prepared in the form of a fast-dissolving tablet, which would also preferably include highly soluble salt forms of the active ingredient.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure or *in vacuo* means that a rotary evaporator was used.

General Experimentals

General Example:

Compounds of the formula I can be prepared by reacting the appropriate compound of formula III with a urea of the formula II (i.e., $\text{H}_2\text{N}(\text{CO})\text{-NH}_2$) in the presence of a suitable base, such as an alkoxide base, preferably sodium ethoxide, in a polar solvent, such as an alcoholic solvent, preferably ethanol, at a temperature of 20°C to the boiling point of the solvent, preferably 80°C for 15 minutes to 3 hours.

General Preparation:

A compound of formula III can be prepared by reacting an appropriate compound of formula IV with a suitable base, such as a tertiary amine base or a polymer bound base, preferably Amberlyst-400® resin (hydroxide form), in a polar solvent, such as an alcoholic solvent, preferably ethanol, at a temperature of about 0°C to about 50°C, preferably about 20°C, for a period of about 6 to about 36 hours.

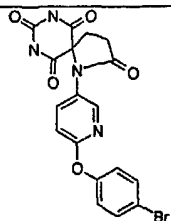
The compound of formula IV can be prepared by reacting the appropriate compound of the formula VI with a compound of the formula V, which has a general formula of $\text{L}^3\text{-(A')-L}^4$ or $\text{L}^3\text{-(A')}$, in an aprotic solvent, preferably and aromatic hydrocarbon solvent such as benzene or toluene, at a temperature of about 40°C and the boiling point of the solvent, preferably about 80°C, for a period of about 1 to about 6 hours.

The compound of formula VI can be prepared by reacting the appropriate compound of the formula $\text{NH}_2\text{-X-Y-Z-G}$ with a compound of the formula VII, which is a 2-halo malonate ester, preferably 2-bromodiethyl malonate, in the presence of a suitable base, such as a tertiary amine base, preferably *N,N*-dimethylaniline, at a temperature of about 20°C to about 100°C, preferably about 80°C, for a period of about 4 to about 48 hours.

EXAMPLE 1:

25 **1-[6-(4-BROMO-PHENOXY)-PYRIDIN-3-YL]-1,7,9-TRIAZA-SPIRO[4.5]DECANE-**

2,6,8,10-TETRAONE:

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
1		445.238	445

Sodium metal (29 mg, 1.26 mmol) was added to 1.3 mL of ethanol and stirred until homogeneous. of 1-[6-(4-Bromo-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.20 g, 0.42 mmol) was added, followed by urea (75 mg, 1.26 mmol) and the mixture

was stirred for 5 minutes at 80 °C. The mixture was cooled to ambient temperature, acidified with 1M hydrochloric acid and extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (3:1 hexane-ethyl acetate), affording 28 mg of 1-[6-(4-Bromo-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone as a colorless solid. HPLC Ret. time: 2.201 min; MS (APCI, m/z): 436 [M-H]⁻; 438 [M+H]⁺.

Preparation 1:

2-(4-Bromo-phenoxy)-5-nitro-pyridine:

4-Bromophenol (5.5 g, 32 mmol) was added to 42 mL of 50% w/w aqueous sodium hydroxide. After stirring for 30 min, 44 mL of toluene was added, followed by 2-chloro-5-nitropyridine (5.0 g, 32 mmol) and tetrabutylammonium bromide (10 g, 32 mmol). After stirring for 1.5 hours at 23°C, the mixture was diluted with 200 mL of water, neutralized with 12M aqueous hydrochloric acid and the mixture was extracted 3x with ether. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*, affording 6 g of 2-(4-bromo-phenoxy)-5-nitro-pyridine. ¹H NMR (CDCl₃, 500 MHz): 9.05 (d, 1H, J = 3.5 Hz), 8.51 (dd, 1H, J = 3.5, 9.5 Hz), 7.58 (d, 2H, J = 9.0 Hz), 7.08 (m, 3H) ppm. MS (APCI, m/z): 295 [M+H]⁺.

6-(4-Bromo-phenoxy)-pyridin-3-ylamine:

A mixture of 2-(4-bromo-phenoxy)-5-nitro-pyridine (6.0 g, 22.7 mmol), 200 mL of methanol and 50 mg of PtO₂ was shaken under 50 psi of H₂ for 1 hour at 23 °C. The mixture was filtered through a pad of celite® and the filtrate was concentrated *in vacuo*, affording 6 g of 6-(4-bromo-phenoxy)-pyridin-3-ylamine. ¹H NMR (CD₃OD, 500 MHz): 7.65 (d, 1H, J = 3.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.25 (dd, 1H, J = 3.5, 9.0 Hz), 6.91 (d, 2H, J = 9.0 Hz), 6.80 (d, 1H, J = 9.0 Hz) ppm. MS (APCI, m/z): 265 [M+H]⁺.

Preparation 2:

1-[6-(4-Bromo-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

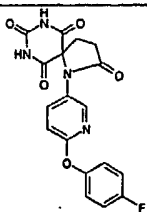
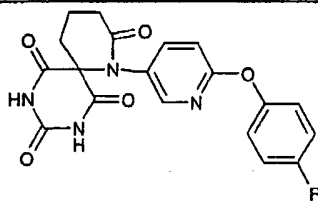
A mixture of 6-(4-bromo-phenoxy)-pyridin-3-ylamine (4.5 g, 16.9 mmol), 2-bromodimethylmalonate (4.1 g, 17 mmol) and *N,N*-dimethylaniline (2.1 g, 17 mmol) was stirred at 80 °C for 24 hours. The mixture was cooled to 23 °C, diluted with 50 mL of benzene and was treated with 7 mL of 2-bromopropionyl chloride. After stirring at reflux for 3 h, the mixture was cooled to 23 °C, concentrated *in vacuo* and was diluted with 750 mL of ethanol. Amberlyst-400 (hydroxide form) resin (75 g) was added and the mixture was stirred for 24 hours at 23 °C. The mixture was filtered and the resin was washed with 50 mL of methanol. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography (2:1 hexane-ethyl acetate), affording 6 g of 1-[6-(4-bromo-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester. ¹H NMR (CDCl₃, 500 MHz): 8.06 (d, 1H, J = 2.5 Hz), 7.75 (dd, 1H, J = 2.5, 8.0 Hz), 7.52 (d, 2H, J = 9.0 Hz), 7.04 (d, 2H, J = 8.5 Hz), 6.95

(d, 1H, J = 9.0 Hz), 4.22 (q, 4H, J = 7.0 Hz), 2.75 (m, 2H), 2.66 (m, 2H), 1.12 (t, 6H, J = 7.5 Hz) ppm. MS (APCI, m/z): 479 [M+H]⁺.

The following compounds were prepared according to methods analogous to that of Example 1, substituting where appropriate the correct pyridine and diester:

5

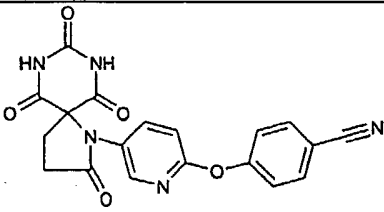
TABLE 1

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
2		384.327	385.1
3		398.354	399.1

Example 4

4-[5-(2,6,8,10-TETRAOXO-1,7,9-TRIAZA-SPIRO[4.5]DEC-1-YL)-PYRIDIN-2-YLOXY]-

BENZONITRILE:

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
4		391.346	392.1

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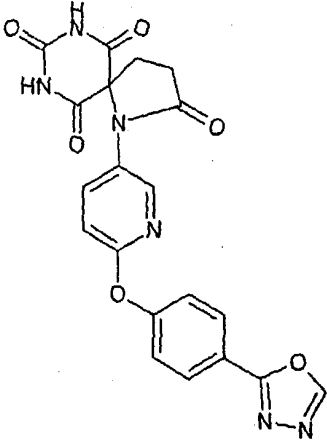
Following the procedure for pyrimidinetrione formation outlined in Example 1, reaction of 1-[6-(4-Cyano-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (58 mg, 0.14 mmol) with urea (0.030 g, 0.5 mmol) in 0.5 mL of 1M sodium ethoxide in ethanol afforded 14.3 mg of 4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile as a colorless solid. ¹H NMR (CD₃OD, 500 MHz): 8.06 (d, 1H, J = 3.5 Hz), 7.78 (m, 3H), 7.31 (d, 2H, J = 8.5 Hz), 7.13 (d, 1H, J = 9.0 Hz), 2.75 (m, 2H), 2.68 (m, 2H) ppm. MS (APCI, m/z): 390 [M-H]⁻; 392 [M+H]⁺.

15

Preparation 1:**1-[6-(4-Cyano-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:**

A mixture of 1-[6-(4-bromo-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.28 g, 0.53 mmol), zinc cyanide (0.037 g, 0.32 mmol), tetrakis(triphenylphosphine) palladium (0) (0.024 g, 0.021 mmol) and 0.66 mL of dimethylformamide was heated to 80 °C for 24 hours. An additional 37mg of zinc cyanide and 24 mg of tetrakis(triphenylphosphine) palladium (0) was added and the mixture was stirred at 80 °C for an additional 48 hours. After cooling to room temperature, the mixture was diluted with toluene and was washed with 2M ammonium hydroxide (twice), brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. Purification by radial chromatography (ethyl acetate-hexanes, then methanol) afforded 58 mg of 1-[6-(4-Cyano-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup. ¹H NMR (CDCl₃, 500 MHz): 8.07 (d, 1H, J = 3.5 Hz), 7.80 (dd, 1H, J = 2.5, 9.0 Hz), 7.69 (d, 2H, J = 9.0 Hz), 7.25 (d, 2H, J = 9.0 Hz), 7.02 (d, 1H, J = 9.0 Hz), 4.21 (q, 4H, J = 7.5 Hz), 2.74 (m, 2H), 2.66 (m, 2H), 1.19 (t, 6H, J = 7.0 Hz) ppm. MS (APCI, m/z): 424 [M+H]⁺.

Example 5**1-[6-(4-[1,3,4]OXADIAZOL-2-YL-PHENOXY)-PYRIDIN-3-YL]-1,7,9-TRIAZA-SPIRO[4.5]DECANE-2,6,8,10-TETRAONE:**

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
5		434.371	435.1

Following the procedure for pyrimidinetrione formation outlined in Example 1, reaction of 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (200 mg, 0.44 mmol) with urea (0.080 g, 1.3 mmol) in 1.3 mL of 1M sodium ethoxide in ethanol afforded 25 mg of 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone as a colorless solid. ¹H NMR (CD₃OD, 500 MHz): 9.02 (s, 1H), 8.14 (d, 2H, J = 8.0 Hz), 8.06 (d, 1H, J = 2.0 Hz), 7.78 (dd, 1H, J = 2.5, 9.0 Hz),

7.35 (d, 2H, J = 9.0 Hz), 7.12 (d, 1H, J = 9.0 Hz), 2.74 (m, 2H), 2.66 (m, 2H) ppm. MS (APCI, m/z): 435 [M+H]⁺.

Preparation 1:

1-[6-(4-Carboxy-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl

5 ester:

A mixture of 1-[6-(4-Formyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.70 g, 1.64 mmol), sodium carbonate (0.26 g, 1.64 mmol) and 16.4 mL of 1:1 *tert*-butyl alcohol-water was treated with potassium permanganate (0.26 g, 1.64 mmol). After stirring for 2 hours at room temperature, the mixture was quenched with sodium sulfite, 10 acidified with 1M hydrochloric acid and extracted 3x with ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*, affording 1-[6-(4-Carboxy-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup (0.5 g). ¹H NMR (CDCl₃, 500 MHz): 8.14 (d, 2H, J = 8.5 Hz), 8.10 (d, 1H, J = 3.0 Hz), 7.80 (dd, 1H, J = 2.5, 8.5 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.02 (d, 1H, J = 9.0 Hz), 4.21 15 (q, 4H, J = 7.0 Hz), 2.74 (m, 2H), 2.66 (m, 2H), 1.21 (t, 6H, J = 7.5 Hz) ppm. MS (APCI, m/z): 443 [M+H]⁺.

Preparation 2:

1-[6-(4-Hydrazinocarbonyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

20 A mixture of affording 1-[6-(4-Carboxy-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.4 g, 0.97 mmol), 1-hydroxybenzotriazole hydrate (0.176 g, 1.3 mmol), 1,2-dichloroethane (0.25 g, 1.3 mmol) and 6 mL of methylene chloride was stirred at room temperature for 20 minutes. The mixture was treated with boc-hydrazide (0.17 g, 1.3 mmol) and stirred at room temperature overnight. The mixture was diluted with ethyl acetate, 25 washed with 1M hydrochloric acid, sodium bicarbonate solution, brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was dissolved in 5 mL of 1:1 v/v methylene chloride-trifluoroacetic acid, stirred for 1 hours at ambient temperature and was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with 1M sodium hydroxide, brine, dried over sodium sulphate, filtered and concentrated, affording 1-[6-(4- 30 Hydrazinocarbonyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.20 g) as a colorless syrup. HPLC: 2.770 min.

Preparation 3:

1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

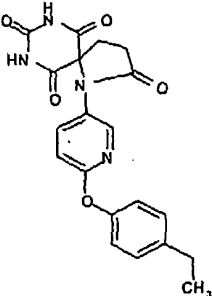
35 A mixture of affording 1-[6-(4-Hydrazinocarbonyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.20 g, 0.44 mmol), trimethylorthoformate (0.1 mL, 0.91 mmol) and 1 mL of xylenes was refluxed for 24 hours. The mixture was

concentrated *in vacuo*, affording 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.2 g) as a colorless syrup. MS (APCI, *m/z*): 467.2 $[M+H]^+$.

Example 6

5

1-[6-(4-ETHYL-PHENOXY)-PYRIDIN-3-YL]-1,7,9-TRIAZA-SPIRO[4.5]DECANE-2,6,8,10-TETRAONE:

Example Number	Structure	Molecular Weight	MS (APCI, <i>m/z</i>): $[M+H]^+$
6		394.39	395.3

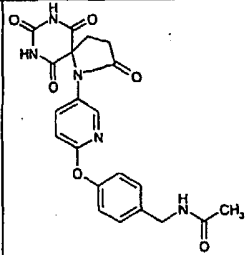
Following the procedure for pyrimidinetrione formation outlined in Example 1, reaction of 1-[6-(4-ethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (200 mg, 0.41 mmol) with urea (0.088 g, 1.4 mmol) in 1.4 mL of 1M sodium ethoxide in ethanol afforded 25 mg of 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone as a colorless solid. ¹H NMR (CDCl₃, 500 MHz): 8.73 (bs, 2H), 7.97 (d, 1H, *J* = 2.0 Hz), 7.78 (d, 1H, *J* = 8.5 Hz), 7.22 (d, 2H, *J* = 8.5 Hz), 7.05 (d, 2H, *J* = 9.0 Hz), 6.91 (d, 1H, *J* = 9.0 Hz), 2.81 (q, 2H, *J* = 7.5 Hz), 2.74 (m, 2H), 2.64 (m, 2H), 1.26 (t, 3H, *J* = 8.0 Hz) ppm.

Preparation 1:

1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

A mixture of 1-[6-(4-vinyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.20 g), 50 mg of 10% palladium on charcoal and 20 mL of ethyl acetate was shaken under 50 psi of hydrogen gas for 2 hours. The mixture was filtered and concentrated *in vacuo*, affording 0.20 g of 1-[6-(4-ethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup. ¹H NMR (CDCl₃, 500 MHz): 8.08 (d, 1H, *J* = 2.5 Hz), 7.73 (dd, 1H, *J* = 2.5, 8.5 Hz), 7.24 (d, 2H, *J* = 7.5 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 9.0 Hz), 4.21 (q, 4H, *J* = 7.0 Hz), 2.74 (m, 2H), 2.65 (m, 4H), 1.27 (t, 3H, *J* = 8.0 Hz), 1.20 (t, 6H, *J* = 7.5 Hz) ppm.

Example 7**N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-acetamide:**

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
7		437.415	438.2

5 A mixture of 1-[6-[4-(tert-butoxycarbonylamino-methyl)-phenoxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.52 mmol) and 2 mL of a 1:1 v/v solution of trifluoroacetic acid in methylene chloride was stirred for 1 hours at ambient temperature and was then concentrated *in vacuo*. The residue was dissolved in 2.6 mL of methylene chloride and was treated with MMP-resin (polymer bound N-methyl morpholine-type base, 0.86 g, 1.75

10 mmol) and was treated with acetyl chloride (0.055 g, 0.7 mmol). After shaking for 24 h, the mixture was filtered and the resin was washed with methylene chloride. The combined filtrates were concentrated *in vacuo*, dissolved in 1.5 mL of 1M sodium ethoxide in ethanol and treated with 94 mg of urea. After stirring for 10 minutes at 80 °C, the mixtures were treated with 2 g of a polystyrene-bound sulfonic acid resin, filtered and the resin was washed with 10

15 mL of 2M ammonia in methanol. The combined filtrates were concentrated *in vacuo* and purified by reverse-phase chromatography (acetonitrile-water-trifluoroacetic acid eluent) followed by radial chromatography (10% methanol-methylene chloride), affording: N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-acetamide as a colorless solid. HPLC Ret. time: 2.201 min; MS (APCI, m/z): 436 [M-H]⁻; 438 [M+H]⁺.

20 Preparation 1:**1-[6-(4-vinyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:**

A mixture of 1-[6-(4-bromo-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (5.8 g, 12.2 mmol), vinyltributyltin (3.9 mL, 12.3 mmol), tetrakis(triphenylphosphine) palladium (0) (0.60 g, 0.52 mmol) and 24 mL of toluene was heated to reflux for 1 hour. After

25 cooling to room temperature, the mixture was concentrated *in vacuo* and purified by silica gel chromatography (Flash 40, 20% - 50% ethyl acetate-hexanes), affording 4.8 g of 1-[6-(4-Vinyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup.

Preparation 2:1-[6-(4-Formyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

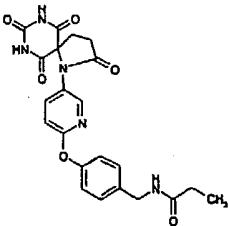
A mixture of 1-[6-(4-Vinyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (4.8 g, 11.3 mmol), sodium metaperiodate (4.8 g, 22 mmol), osmium tetroxide (10 mg) and 2:1 dioxane-water (189 mL) was stirred for 6 hours at ambient temperature. The mixture was quenched with sodium sulfite, diluted with water and extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo*, affording 1-[6-(4-Formyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup (4.6 g).

Preparation 3:1-[6-[4-(tert-Butoxycarbonylamino-methyl)-phenoxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

A mixture of 1-[6-(4-Formyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.1 g, 0.24 mmol), *tert*-butoxycarbonylamide (0.083 g, 0.71 mmol), triethylsilane (0.11 mL, 0.083 g, 0.71 mmol) and acetonitrile (1 mL) was treated with trifluoroacetic acid (0.035 mL, 0.46 mmol) and stirred for 48 at ambient temperature. The mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, brine, dried over sodium sulphate, filtered and concentrated *in vacuo*, affording 1-[6-[4-(tert-Butoxycarbonylamino-methyl)-phenoxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup.

The following compounds were prepared according to methods analogous to that of Example 7, submitting where appropriate the correct pyridine and diester:

TABLE 2

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
8		451.443	452.2

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
9		465.47	466.2
10		479.497	480.2
11		477.481	478.4

Example 12

**1-[6-(4-PYRAZOL-1-YLMETHYL-PHENOXY)-PYRIDIN-3-YL]-1,7,9-TRIAZA-
SPIRO[4.5]DECANE-2,6,8,10-TETRAONE:**

Example Number	Structure	Molecular Weight	MS (APCI, m/z): [M+H] ⁺
12		446.43	447.2

Following the procedure for pyrimidinetrione formation outlined in Example 1, reaction of 5-oxo-1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.2 g, 0.4 mmol) with urea (0.074 g, 1.2 mmol) in 1.2 mL of 1M sodium ethoxide in ethanol afforded 6 mg of 1-[6-(4-Pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,7,9-triazaspiro[4.5]decane-2,6,8,10-tetraone as a colorless solid. ¹H NMR (CD₃OD, 500 MHz): 7.99 (d, 1H, J = 2.5 Hz), 7.72 (m, 2H), 7.53 (d, 1H, J = 2.5 Hz), 7.29 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.5 Hz), 6.97 (d, 1H, J = 8.5 Hz), 6.35 (t, 1H, J = 2.0 Hz), 5.38 (s, 2H), 2.75 (m, 2H), 2.65 (m, 2H) ppm. MS (APCI, m/z): 447.2 [M+H]⁺.

Preparation 1:

10 1-[6-(4-Hydroxymethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

15 1-[6-(4-Hydroxymethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester: To a solution of 1-[6-(4-formyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (1.0 g, 2.3 mmol) in 30 mL of ethanol was added sodium borohydride (0.090 g, 2.3 mmol) at 0 °C. After stirring for 3 hours, the mixture was concentrated *in vacuo*, diluted with ethyl acetate and water, and the aqueous layer was cautiously acidified with 1M hydrochloric acid, then neutralized with saturated aqueous sodium bicarbonate. The mixture was extracted three times with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording 0.80 g (80%) of 1-[6-(4-hydroxymethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup. ¹H NMR (CDCl₃, 400 MHz): 8.04 (d, 1H, J = 2.4 Hz), 7.72 (dd, 1H, J = 2.4, 8.8 Hz), 7.40 (d, 2H, J = 8.8 Hz), 7.12 (d, 2H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.8 Hz), 4.70 (s, 2H), 4.19 (q, 4H, J = 7.6 Hz), 2.75 (m, 2H), 2.65 (m, 2H), 1.18 (t, 6H, J = 7.2 Hz) ppm. MS (APCI, m/z): 429.1 [M+H]⁺.

25 Preparation 2:

1-[6-(4-Bromomethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

 To a solution of 1-[6-(4-hydroxymethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.80 g, 1.9 mmol) in 9.4 mL of methylene chloride was added triethylamine (0.46 mL, 0.33 g, 3.3 mL). After cooling to -40 °C, the mixture was treated with methanesulfonyl chloride (0.20 mL, 0.30 g, 2.61 mmol). After stirring for 1 hour, an additional 0.10 mL of methanesulfonyl chloride and 0.4 mL of triethylamine were added, and stirring was continued for 1 hour. A solution of anhydrous lithium bromide (1.6 g, 19 mmol, flame dried under vacuum before use) in tetrahydrofuran (20 mL) was added via cannula, and the mixture was warmed to room temperature and stirred for 2 hours. The mixture was diluted with ethyl acetate, and the organic phase was washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel eluting with 1:1

ethyl acetate-hexanes, affording 0.65 g of 1-[6-(4-bromomethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester as a colorless syrup. ¹H NMR (CDCl₃, 500 MHz): 8.07 (d, 1H, J = 3.0 Hz), 7.76 (dd, 1H, J = 2.5, 8.5 Hz), 7.44 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.0 Hz), 6.95 (d, 1H, J = 9.0 Hz), 4.53 (s, 2H), 4.22 (q, 4H, J = 7.0 Hz), 2.75 (m, 2H), 2.65 (m, 2H), 1.20 (t, 6H, J = 7.0 Hz) ppm.

Preparation 3:

5-Oxo-1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester:

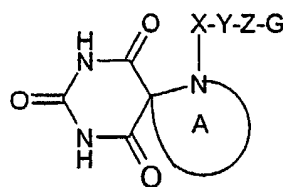
To a solution of 1-[6-(4-bromomethyl-phenoxy)-pyridin-3-yl]-5-oxo-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.2 g, 0.4 mmol) in 0.8 mL of dimethylformamide was added pyrazole (0.056 g, 0.82 mmol) and potassium carbonate (0.11 g, 0.82 mmol). After stirring for 24 hours at 50 °C, the mixture was diluted with water, extracted three times with ethyl acetate, and the combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*, affording the crude product as a colorless syrup that was used directly in the next step.

MS (APCI, m/z): 479.2 [M+H]⁺.

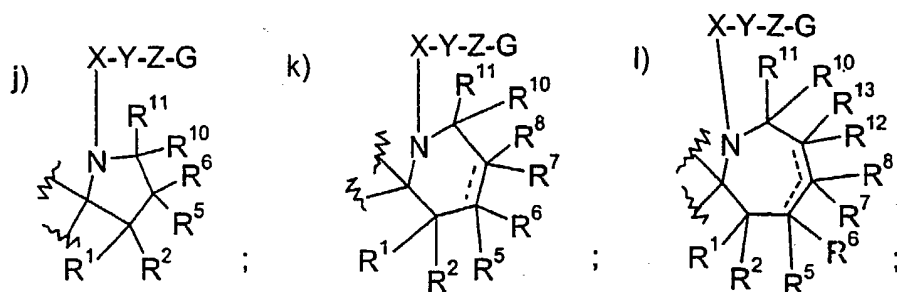
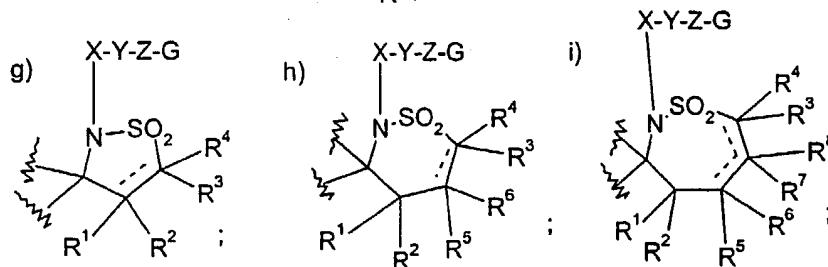
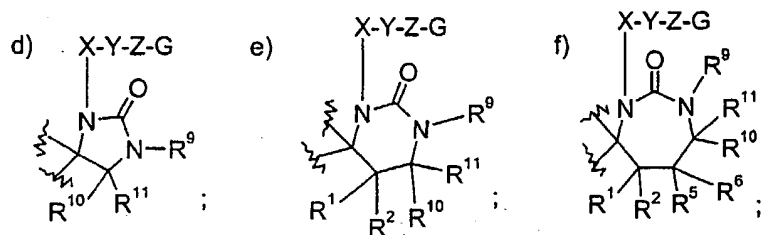
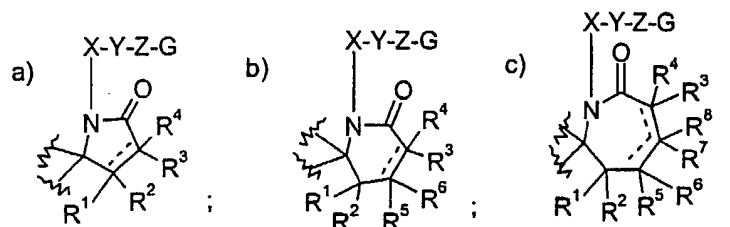
While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

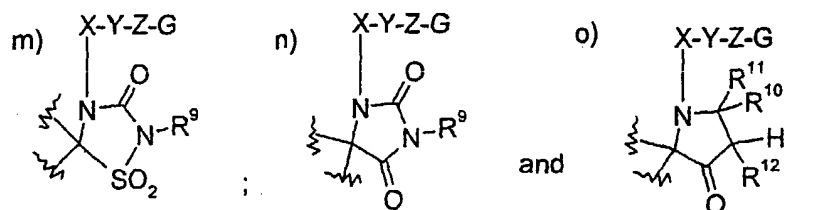
We Claim:

1. A compound of the formula:



wherein said "A" is a 5-7 membered heterocyclic ring selected from the group consisting of:





wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} is independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl; wherein each of said (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond with 1-3 substituents per ring independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -CN, -OH and -NH₂;

X is (C₆-C₁₀)aryl or (C₁-C₁₀)heteroaryl;

Y is selected from the group consisting of a bond, oxygen, sulfur, >C=O, >SO₂, >S=O, -CH₂-, -CH₂O-, -O(CH₂)_n-, -CH₂S-, -S(CH₂)_n-, -CH₂SO-, -CH₂SO₂-, -SO(CH₂)_n-, -SO₂(CH₂)_n-, -NR¹⁴-, -NR¹⁴(CH₂)_n-, -CH₂[N(R¹⁴)]-, -CH₂(CH₂)_n-, -CH=CH-, -C≡C-, -[N(R¹⁴)]-SO₂- and -SO₂[N(R¹⁴)]-;

n is an integer from one to four;

R¹⁴ is hydrogen or (C₁-C₄)alkyl;

Z is selected from the group consisting of (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heterocyclyl and (C₁-C₁₀)heteroaryl; wherein one or two carbon-carbon single bonds of said (C₃-C₈)cycloalkyl or (C₁-C₁₀)heterocyclyl may optionally be replaced by carbon-carbon double bonds;

wherein each of said X or Z may be independently optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy;

G is R¹⁵-(CR¹⁶R¹⁷)_p; wherein G is a substituent on any ring carbon atom of Z capable of forming an additional bond and is oriented at a position other than alpha to the point of attachment of the Z ring to Y;

p is an integer from 0 to 4;

R¹⁵ is independently selected from the group consisting of halo, -CN, -NO₂, OH, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₁-C₄)perfluoroalkyl, perfluoro(C₁-C₄)alkoxy, R¹⁸-, R¹⁸-O-, R¹⁸-(C₁-C₄)alkyl-O-, R¹⁸-(C=O)-, R¹⁸-(C=O)-O-, R¹⁸-O-(C=O)-, R¹⁸-S-, R²²-(S=O)-, R¹⁸-(SO₂)-, R²²-(SO₂)-(NR²¹)-, R¹⁹-(C=O)-(NR²¹)-, R²²-O-(C=O)-(NR²¹)-, (R¹⁹R²⁰)N-, (R¹⁹R²⁰)N-(SO₂)-, (R¹⁹R²⁰)N-(C=O)-, (R¹⁹R²⁰)N-(C=O)-(NR²¹)- and (R¹⁹R²⁰)N-(C=O)-O-;

each of R¹⁶ and R¹⁷ are independently selected from hydrogen and (C₁-C₄)alkyl;

or R¹⁶ and R¹⁷ may optionally be taken together with the carbon to which they are attached to form a 5 to 10-membered carbocyclic ring;

R¹⁸, R¹⁹, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

or R¹⁹ and R²⁰ may optionally be taken together with the nitrogen to which they are attached to form a 3 to 8-membered heterocyclic ring;

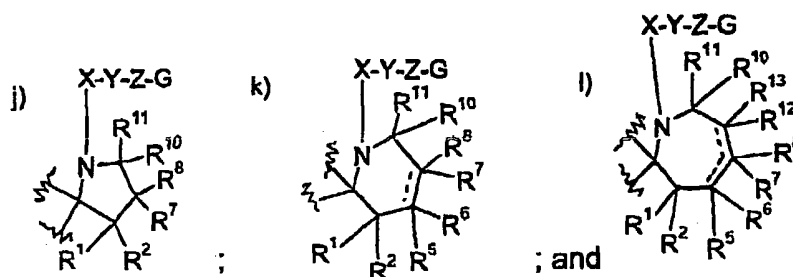
or R¹⁹ and R²¹ may optionally be taken together with the nitrogen, the carbon or the oxygen to which they are attached to form a 3 to 8-membered heterocyclic ring;

R²² is selected from the group consisting of (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; wherein said (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may be optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, amino, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl moieties may also optionally be substituted by oxo; wherein said (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl moieties may optionally be substituted on any ring nitrogen atom able to support an additional substituent by one to two substituents per ring independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

or R²¹ and R²² may optionally be taken together with the nitrogen, the oxygen or the sulfur to which they are attached to form a 3 to 8-membered heterocyclic ring;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein said "A" is selected from the group consisting of



3. The compound according to claim 1 wherein said X is (C₆-C₁₀)aryl.
4. The compound according to claim 1 wherein said X is (C₁-C₁₀)heteroaryl.
5. The compound according to claim 1 wherein said Y is oxygen.
- 5 6. The compound according to claim 1 wherein said G is R¹⁵-(CR¹⁶R¹⁷)_p;
wherein p is 0.
7. The compound according to claim 1 wherein said G is R¹⁵-(CR¹⁶R¹⁷)_p;
wherein p is an integer from 1 to 4.
8. A compound according to claim 1, wherein said compound is selected from
10 the group consisting of:
1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
1-[6-(4-Fluoro-phenoxy)-pyridin-3-yl]-1,8,10-triaza-spiro[5.5]undecane-2,7,9,11-
tetraone;
4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzonitrile;
15 1-[6-(4-[1,3,4]oxadiazol-2-yl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-
2,6,8,10-tetraone;
1-[6-(4-Ethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
acetamide;
20 N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
propionamide;
N-[4-[5-(2,6,8,10-Tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzyl]-
butyramide;
Pentanoic acid 4-[5-(2,6,8,10-tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-
25 benzylamide;
Cyclobutanecarboxylic acid 4-[5-(2,6,8,10-tetraoxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-
pyridin-2-yloxy]-benzylamide;
1-[6-(4-Bromo-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-2,6,8,10-tetraone;
1-[6-(4-pyrazol-1-ylmethyl-phenoxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-
30 2,6,8,10-tetraone;
and a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition for the treatment of a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

10. A method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

15 11. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

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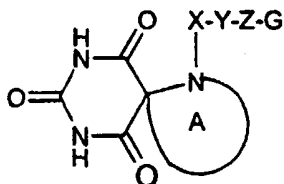
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WO 02/034753 A3

(54) Title: SPIRO-PYRIMIDINE-2,4,6-TRIONE METALLOPROTEINASE INHIBITORS



(A)

(57) Abstract: The present invention relates to 5-spiro-pyrimidine-2,4,6-trione metalloproteinase inhibitors of the formula wherein said "A" is a 5-7 membered heterocyclic ring as defined in the specification and to pharmaceutical compositions and methods of treating inflammation, cancer and other disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/01986

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/10 A61K31/527 A61P29/00 A61P35/00 C07D471/10
 //(C07D487/10,239:00,209:00),(C07D471/10,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 47565 A (HOFFMANN LA ROCHE) 17 August 2000 (2000-08-17) cited in the application page 1, line 14 - line 20; claim 1 ---	1,9,11
A	WO 98 58925 A (BOEHRINGER) 30 December 1998 (1998-12-30) cited in the application claim 1; table 1 ---	1,9,11
A	US 3 714 093 A (WOLF M ET AL) 30 January 1973 (1973-01-30) column 2, line 50 -column 3, line 31; claim 1 ---	1,9
P,A	WO 01 12611 A (PFIZER) 22 February 2001 (2001-02-22) claims 1,35,37 -----	1,9,11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/01986

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 IS directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
information on patent family members

International Application No

PCT/IB 01/01986

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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(54) **The use of MMP-13 selective inhibitors for the treatment of osteoarthritis and other matrix metalloproteinase-mediated disorders**

(57) The present invention relates to the use of matrix metalloproteinase-13 selective agents for the treat-

ment or prevention of osteoarthritis and other matrix metalloproteinase-mediated disorders.

USPN: 10/071,032 Filed: 02/08/2002 Art Unit: 1624
Docket: A0000425-01-CPP Inventor: R. Dyer, et al.

EP 0 935 963 A2

Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to the use of matrix metalloproteinase inhibitors which display specificity for matrix metalloproteinase-13 versus matrix metalloproteinase-1. These compounds are useful in the treatment or prevention of osteoarthritis, rheumatoid arthritis and cancer.

[0002] Osteoarthritis and rheumatoid arthritis are joint diseases which are characterized by cartilage damage and loss of joint function, which may eventually culminate in joint replacement. One of the principal biochemical events in such joint diseases is damage to and subsequent loss of type II collagen, the predominant articular cartilage collagen. Type II collagen is extremely resistant to proteolytic cleavage, with the collagenases of the matrix metalloproteinase (MMP) family being the only mammalian enzymes with the ability to cleave the native, helical type II, collagen present in normal cartilage.

[0003] Three type II collagen degrading matrix metalloproteinases are currently known, MMP-1, MMP-8 and MMP-13. These matrix metalloproteinases are also known as collagenases 1, 2 and 3, respectively. Matrix metalloproteinase-1, collagenase-1, is expressed throughout the body by a wide variety of connective tissues including osteoarthritic cartilage and synovium. Mitchell *et al.*, *J. Clin. Invest.*, 97, 761-768 (1996) and Wolfe *et al.*, *Arthritis Rheum.*, 36, 1540-1547 (1993). Matrix metalloproteinase-8, collagenase-2, was initially thought to be expressed exclusively by neutrophils. However, recent evidence demonstrates that low levels of MMP-8 mRNA and protein are present in human cartilage and it has been suggested that this enzyme may participate in aggrecan degradation, Chubinskaya *et al.*, *Lab. Invest.*, 74, 232-240 (1993) and Cole *et al.*, *J. Biol. Chem.*, 271, 11023-11026 (1996). Matrix metalloproteinase-13, collagenase-3, originally reported in a breast carcinoma cell line, is the most recent member of this class to be discovered, Freije *et al.*, *J. Biol. Chem.*, 269, 16766-16773 (1994). The present inventors independently cloned collagenase-3 from human osteoarthritic cartilage and have demonstrated that this new matrix metalloproteinase is expressed at substantial levels in human osteoarthritic cartilage, Mitchell *et al.*, *J. Clin. Invest.*, 97, 761-768 (1996).

[0004] Matrix metalloproteinase inhibitors, i.e. compounds which broadly inhibit MMPs including MMP-1 MMP-8 and MMP-13, are known and have been used to demonstrate that non-selective MMP inhibitors block cartilage collagen degradation in *in vitro* cartilage explant systems. Nixon *et al.*, *Int. J. Tiss. React.*, 13, 237-243 (1991); Mitchell *et al.*, *Annals. New York Acad. Sci.*, 732, 395-397 (1994), and Mort *et al.*, *Matrix.*, 13, 95-102 (1993).

[0005] Until recently, MMP-1 was the only collagenase known to be expressed by cartilage and other connective tissues and, as a result, has been the subject of the most collagenase research. As stated above, comprehensive tissue distribution studies have demonstrated that MMP-1 can be expressed by a variety of tissues especially those involved in connective tissue collagen homeostasis such as skin, gingiva, meniscus, tendon and ligament.

[0006] The present inventors have now discovered that MMP-13, contrary to MMP-1, is not expressed in any of these tissues, (e.g., skin, gingiva, meniscus, tendon and ligament), even under conditions (e.g., interleukin-1 stimulation) in which MMP-1 is substantially upregulated. The only tissue with significant MMP-13 expression is cartilage.

[0007] Furthermore, the present inventors have also demonstrated that, *in vitro*, collagenase-3 has ten fold greater activity against type II collagen than does collagenase-1, *J. Clin. Invest.*, supra. However, *in vitro* activity of the collagenases is not necessarily indicative of the biological role of each of these agents, because both enzymes exist in a pro-active form that is converted to the active species by mechanisms that have yet to be clearly elucidated *in vivo*. In addition, natural inhibitors (e.g., the tissue inhibitors of metalloproteinases or TIMPs) can differentially regulate MMP activity. Thus, in the absence of data demonstrating that compounds with selectivity for MMP-13 versus MMP-1 eliminate type II collagen degradation, it would be speculative to conclude that such a selective inhibitor could be useful to treat or prevent osteoarthritis and other matrix metalloproteinase mediated disorders.

[0008] The present inventors have surprisingly discovered that even though collagenase-1 and collagenase-3 are present in activated cartilage, inhibitors with specificity for collagenase-3 versus collagenase-1 blocked substantially all type II collagen degradation at concentrations indicative of collagenase-3 inhibition but not collagenase-1 inhibition. This is so surprising, because one of ordinary skill in the art would have expected that a MMP-13 selective inhibitor would either have no effect or would have only a partial effect on collagen degradation. This is so, because MMP-1 was thought to be the principal collagen degrading enzyme in cartilage and thus the uninhibited MMP-1 would have been expected to continue degrading collagen. However, as the data below demonstrate, such is not the case.

[0009] Furthermore, recent clinical trial data for marimastat, a non-selective MMP-1 and MMP-13 inhibitor, revealed significant dose-related connective tissue side effects, likely due to inhibition of normal connective tissue collagen turnover by systemic inhibition of MMP-1, *Proceedings of ASCO*, 15, 490 (1996). Such connective tissue toxicity significantly limits the therapeutic applications of such MMP-1/MMP-13 inhibitors. Based on the tissue distribution studies, that demonstrate that MMP-13 is almost exclusively expressed in cartilage while MMP-1 is broadly expressed, it is expected that systemic inhibition of MMP-13 will not produce the connective tissue toxicity limiting the use of non-selective MMP-1/MMP-13 inhibitors. Thus, in conjunction with the collagenase inhibition data referred to above, the

present inventors have discovered that compounds with MMP-13 versus MMP-1 activity are surprisingly superior inhibitors of cartilage collagen degradation that will act without producing systemic connective tissue toxicity.

[0010] Matrix metalloproteinase inhibitors, i.e. agents which broadly inhibit matrix metalloproteinases 1, 8 and 13, have been described in the literature. Specifically, PCT publications WO 96/33172, published October 24, 1996, and WO 96/27583, published March 7, 1996, refer to hydroxamic acids which inhibit matrix metalloproteinases.

[0011] PCT Application No. PCT/US95/07166, filed June 07, 1995 (which corresponds to United States Patent Application No. 60/017850, filed May 20, 1996), refers to other hydroxamic acids which inhibit matrix metalloproteinases.

[0012] United States Patent Application No. 60/021,652, filed July 12, 1996; United States Patent Application No. 60/024,675, filed August 23, 1996; United States Patent Application No. 60/021,959, filed July 18, 1996; United States Patent Application No. 60/037,600, filed February 11, 1997; United States Patent Application No. 60/037,402, filed February 7, 1997; United States Patent Application No. 60/036,857, filed February 3, 1997; and United States Patent Application No. 60/034,535, filed January 6, 1997, refer to other hydroxamic acids, glutaramides or phosphinates which also inhibit matrix metalloproteinases.

[0013] European Patent Application 606,046, published July 13, 1994, refers to aryl sulfonamido-substituted hydroxamic acids and states that they are a useful as matrix metalloproteinase inhibitors.

[0014] PCT publication WO 90/05719, published May 31, 1990, refers to other hydroxamic acids and states that they are useful as MMP inhibitors.

[0015] European Patent Publication 780,386, published June 25, 1997, refers to novel matrix metalloproteinase inhibitors. The authors state that, based on tissue distribution of the collagenases, collagenase-3 is the major participant in the degradation of the cartilage collagen matrix and, therefore, inhibitors selective for collagenase-3 over collagenase-1 would be preferred for the treatment of diseases associated with cartilage erosion, such as arthritis. However, the tissue distribution data in this application was very limited and did not include many of the connective tissues that are known producers of MMP-1. In addition, no evidence was presented that inhibitors with selectivity for MMP-13 versus MMP-1 inhibited cartilage collagen degradation.

[0016] German Patent Publication 19,501,032, published July 18, 1996, presents claims to the treatment of rheumatic disorders by inactivating collagenase-3. The authors provide no data to indicate that collagenase-3 was in fact inhibited.

SUMMARY OF THE INVENTION

[0017] The present invention relates to a method of treating or preventing a disorder or condition that can be treated or prevented by selectively inhibiting collagenase-3 with respect to collagenase-1 (preferably without producing systemic connective tissue toxicity) in a mammal, preferably a human, comprising administering to said mammal requiring such treatment or prevention a collagenase-3 inhibiting effective amount of a collagenase-3 selective inhibitor, or pharmaceutically acceptable salts thereof.

[0018] Thus a first aspect of the invention is the use of a collagenase-3 selective inhibitor or a pharmaceutically acceptable salt in the preparation of a medicament for the treatment or prophylaxis of a disorder or condition which can be treated or prevented by selectively inhibiting collagenase-3.

[0019] Preferably the condition of disorder is osteoarthritis.

[0020] The present invention also relates to a method of treating or preventing osteoarthritis in a mammal, preferably a human, comprising administering to said mammal requiring such treatment or prevention a collagenase-3 inhibiting effective amount of a compound selected from the group consisting of:

- 1-([4-(4-fluorophenoxy)benzenesulfonyl]-pyridin-3-ylmethyl-amino)-cyclopentanecarboxylic acid,
- 2-([4-(4-fluorophenoxy)benzenesulfonyl]-pyridin-3-ylmethyl-amino)-N-hydroxy-2 methyl-propionamide,
- (4-benzyl-benzyl)-[2-(2,2-dimethyl-1-methylcarbamoylpropylcarbamoyl)-6-phenoxy-hexyl]-phosphinic acid],
- 2-amino-3-[4-(4-fluorophenoxy)benzenesulfonyl]-N-hydroxypropionamide,
- N-hydroxy-2-[(4-benzoyloxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-acetamide,
- (4-benzyl-benzyl)-(2-[2-(4-methoxy-phenyl)-1-methylcarbamoyl-ethylcarbamoyl]-6-phenoxy-hexyl)-phosphinic acid
- 3-[4-(4-fluorophenoxy)benzenesulfonyl]-2, N-dihydroxypropionamide,
- 2-(1-[4-(4-fluorophenoxy)benzenesulfonyl]-cyclobutyl)-2, N-dihydroxy-acetamide,
- 3-(4-phenoxybenzenesulfonyl)-7-oxa-bicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide,
- 2-[4-(4-fluorophenoxy)benzenesulfonyl-amino]-N-hydroxy-2-methyl-propionamide,
- 1-[4-(4-fluorobenzoyloxy)-benzenesulfonyl]-2-hydroxycarbamoylpiperidine-4-carboxylic acid,
- 4-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-oxobutyric acid,
- 4-[4-(4-chlorophenoxy)benzenesulfonylmethyl]-tetrahydropyran-4-carboxylic acid hydroxyamide,
- (S)- α -[2-(4'-chloro[1,1'-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1, 3-dioxo-2H-isoindole-2-butanolic acid;
- 4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(N-hydroxycarboxamide), and

3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide,
or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Collagenase inhibitors, wherein the MMP-13/MMP-1 selectivity ratio is not known, can be prepared according to methods well known to those of ordinary skill in the art. Specifically, collagenase inhibitors with broad activity and their methods of preparation have been described in WO 96/33172 and WO 96/27583; PCT Application No. PCT/US95/07166 filed June 07, 1995 (which corresponds to United States Patent Application No. 60/017,850); PCT Application No. PCT/B95/00427, filed June 6 1995; EP-A-818442 (United States Patent Application No. 60/021,652); WO 98/07697 (United States Patent Application No. 60/024,675); WO 98/03516 (United States Patent Application No. 60/021,959); WO 98/34918 (United States Patent Application No. 60/037,600); WO 98/34915 (United States Patent Application No. 60/037,402); WO 98/33768 (United States Patent Application No. 60/036,857); WO 98/30566 (United States Patent Application No. 60/034,535); EP-A-606,046; WO 90/05719; and EP-A-780,386. All of the foregoing references are incorporated herein by reference in their entirety.

[0022] Collagenase-3 (matrix metalloproteinase-13) selective inhibitors as used herein refer to agents which exhibit at least a 100 fold selectivity for the inhibition of collagenase-3 enzyme activity over collagenase-1 enzyme activity and a potency of less than 100 nM as defined by the IC_{50} results from the MMP-13/MMP-1 fluorescence assays described below. Collagenase-3 selective inhibitors can be identified by screening collagenase inhibitors, prepared according to the patents and publications described above, through the MMP-13/MMP-1 fluorescence assays described below and selecting those agents with MMP-13/MM-1 inhibition IC_{50} ratios of 100 or greater and potency of less than 100 nM. MMP-13 (collagenase-3) selective inhibitors may possess differential activity towards other MMP's, aggrecanase, TACE, ADAM-10, ADAM-12,

ADAMTS-1 or collagenase 2. One of ordinary skill in the art would know how to assay for these various metalloenzymes. [0023] Collagenase inhibitors as used herein refer to compounds with collagenase inhibiting activity wherein the MMP-13/MMP-1 selectivity is not known.

[0024] Non-selective collagenase inhibitors as used herein refer to agents which exhibit less than a 100 fold selectivity for the inhibition of collagenase-3 enzyme activity over collagenase-1 enzyme activity or a potency of more than 100nM as defined by the IC_{50} results from the MMP-13/MMP-1 fluorescence assays described below.

[0025] The ability of collagenase inhibitors to inhibit collagenase activity is well known in the art. The present inventors are the first to discover the ability of collagenase-3 (matrix metalloproteinase-13) selective inhibitors, preferably the compounds listed above as preferred compounds of the invention or their pharmaceutically acceptable salts (hereinafter also referred to as the active compounds) to inhibit type II cartilage collagen degradation. The following experiments demonstrate: (1) that the compounds do indeed have selectivity for MMP-13 versus MMP-1; (2) MMP-13 selective compounds inhibit substantially all of the collagenase activity released from IL-1 stimulated cartilage explants; and (3) MMP-13 selective compounds inhibit substantially all type II cartilage collagen degradation in cartilage explants.

EXPERIMENT 1

Inhibition of Human Collagenase (MMP-1)

[0026] Human recombinant collagenase-1 is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 μ g trypsin per 100 μ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

[0027] Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following Scheme:

10 mM \rightarrow 120 μ M \rightarrow 12 μ M \rightarrow 1.2 μ M \rightarrow 0.12 μ M

[0028] Twenty-five microliters of each concentration is then added to triplicate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) and negative controls (no enzyme no inhibitors) are also run in triplicate on each plate.

[0029] Collagenase-1 is diluted to 240 ng/ml and 25 μ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

[0030] Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μ M in assay buffer. The assay is initiated by the addition of 50 μ l substrate per well of the microfluor plate to give a final concentration of 10 μ M.

[0031] Fluorescence readings (360 nm excitation, 460 nm emission) are taken at time 0 and then at 20 minute

intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

[0032] Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least 5 fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50} 's are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

[0033] If IC_{50} 's are reported to be less than 0.03 μ M, then the inhibitors are assayed at concentrations of 0.3 μ M, 0.03 μ M, and 0.003 μ M.

Inhibition of MMP-13

[0034] Human recombinant MMP-13 is activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is then diluted to 240 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20 μ M zinc chloride, 0.02% Brij 35). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluo plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 60 ng/ml.

[0035] Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase-1. Twenty-five microliters of each concentration is added to triplicate wells of a microfluo plate. The final concentrations in the assay are 30 μ M, 3 μ M, 0.3 μ M, and 0.03 μ M.

[0036] Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ l is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nM excitation; 450 nM emission) are taken at time 0 and every 5 minutes for 1 hour.

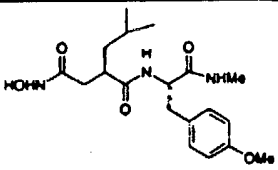
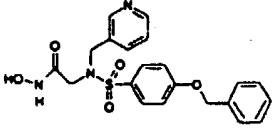
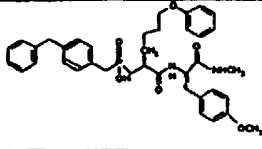
[0037] Positive controls and negative controls are set up in triplicate as outlined in the MMP-1 assay.

[0038] IC_{50} 's are determined as per inhibition of human collagenase (MMP-1). If IC_{50} 's are reported to be less than 0.03 mM, inhibitors are then assayed at final concentrations of 0.3 μ M, 0.03 μ M, 0.003 μ M and 0.0003 μ M.

[0039] Matrix metalloproteinase-13 selective inhibitors are agents that demonstrate an IC_{50} of less than 100 nM in the MMP-13 assay described above. Furthermore, the IC_{50} ratio of MMP-13/MMP-1 inhibition must be greater than 100 fold.

[0040] Application of the above referenced protocols to the broad spectrum inhibitor, Example 1 (prepared according to Example 2 from United States Patent No. 4,599,361, issued July 8, 1986), and two MMP-13 selective compounds, Examples 2 and 3 (prepared according to Example 2 from World Patent Application Serial No. PCT/IB95/00427, filed June 6, 1995, and Example 11 from United States Patent Application Serial No. 09/892,417, filed July 14, 1997 claiming priority from United States Patent Application No. 60/021,959, filed July 18, 1996, respectively) yielded the data reported in Table 1.

TABLE 1

Example	Formula	MMP-1 IC ₅₀ (nM)	MMP-13 IC ₅₀ (nM)
1		2.5	1.5
2		17700	5.4
3		21700	70

EXPERIMENT 2

Collagen film MMP-13 Assay

[0041] The purpose of this second experiment is to: (1) demonstrate that the active agents inhibit collagen degradation and (2) to determine which active collagenases are present in the conditioned medium from cartilage explants undergoing resorption. Only collagenases can degrade helical collagen whereas peptides, such as the substrate described in Experiment 1 above, can potentially be degraded by a variety of proteases. The method described below can be used to verify the fluorescence assay data with respect to the selectivity of inhibitors for MMP-13 versus MMP-1. The principal advantage of this assay over the fluorescence assay is that the natural substrate is used (i.e. collagen) instead of an artificial substrate (e.g., fluorescent peptide substrates). In addition, since collagen is the substrate and since only collagenases can degrade this substrate, collagenase activity in complex mixtures of enzymes (e.g., the conditioned medium from cartilage explants) can be determined. One of ordinary skill in the art will understand that this assay, described below, can be adjusted in many ways to suit the particular needs of an experimenter.

[0042] Rat type I collagen is radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, *Anal. Biochem.*, 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, *Anal. Biochem.*, 104, 175-181 (1980)). When a solution containing collagenase is added to the well, the enzyme cleaves the insoluble collagen which unwinds and is thus solubilized. Collagenase activity is directly proportional to the amount of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors are, therefore, compounds which reduce the radioactive counts released with respect to the controls with no inhibitor present. One specific embodiment of this assay is described in detail below.

[0043] For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure is used. Recombinant human proMMP-13 or proMMP-1 is activated according to the procedures outlined in Experiment 1. The activated MMP-13 or MMP-1 is diluted to 0.6 ug/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂, 1 uM ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

[0044] Stock solutions of test compound (10mM) in dimethylsulfoxide are prepared. Dilutions of the test compounds in the Tris buffer, above, are made to 0.2, 2.0, 20, 200, 2000 and 20000 nM.

[0045] 100 µl of appropriate drug dilution and 100 µl of diluted enzyme are pipetted into wells of a 96 well plate containing collagen films labeled with ¹⁴C-collagen. The final enzyme concentration is 0.3 µg/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control is analyzed in triplicate. Triplicate controls are also run for the conditions in which no enzyme is present and for enzyme in the absence of any compound.

[0046] The plates are incubated at 37°C for a time period such that around 30 - 50% of the available collagen is solubilized - determined by counting additional control wells at various time points. In most cases around 9 hours of

incubation are required. When the assay has progressed sufficiently, the supernatant from each well is removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no enzyme) are subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor. The triplicate values for each point are averaged and the data graphed as percent release versus drug concentration. IC_{50} 's are determined from the point at which 50% inhibition of release of radiolabeled collagen is obtained. IC_{50} 's in this assay (type I collagen) for Examples 1-3 are shown in Table 2.

[0047] To determine the identity of the active collagenases in cartilage conditioned medium, assays were carried out using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying selectivity. The cartilage conditioned medium was collected during the time at which collagen degradation was occurring and thus is representative of the collagenases responsible for the collagen breakdown. Assays were carried out as outlined above except that instead of using recombinant MMP-13 or recombinant MMP-1, cartilage conditioned medium was the enzyme source. The same inhibitors were assayed and their IC_{50} 's are also listed in Table 2. As expected, the equipotent MMP-1/MMP-13 inhibitor, Example 1, was a potent inhibitor of the cartilage collagenase conditioned medium activity. Since the compound is an equipotent inhibitor of both collagenases, it is not possible to determine if one or both enzymes are present as an active species in the conditioned medium. However, surprisingly, the two structurally divergent MMP-13 selective compounds Examples 2 and 3, were also potent inhibitors of the cartilage conditioned medium collagenase activity with IC_{50} 's indicative of MMP-13 being the predominantly active collagenase and not MMP-1.

TABLE 2

Example	MMP-1 Fluor. IC ₅₀ (nM)	MMP-1 Type I Collagen IC ₅₀ (nM)	MMP-13 Fluor. IC ₅₀ (nM)	MMP-13 Type 1 Collagen IC ₅₀ (nM)	Cartilage Conditioned Medium IC ₅₀ (nM)
1	2.5	3.5	1.5	1.5	10
2	17700	22000	5.4	52	220
3	21700	40000	70	40	400

EXAMPLE 3**IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage**

[0048] This third experiment demonstrates that agents with MMP-13/MMP-1 selectivity inhibit substantially all cartilage collagen degradation in cartilage explants. This assay uses bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily type II collagen and aggrecan. The tissue is used because it: (1) is very similar to articular cartilage, (2) is readily available, (3) is relatively homogeneous, and (4) degrades with predictable kinetics after IL-1 stimulation. In addition, the inventors have found that in bovine nasal cartilage, as in human articular cartilage, IL-1 stimulates upregulation of both MMP-1 and MMP-13 mRNA and protein.

[0049] Two variations of this assay have been used to assay compounds. Both variations give similar data. The two variations are described below:

Variation 1

[0050] Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) are placed into each well of a 24 well tissue culture plate. One ml of serumless medium is then added to each well. Compounds are prepared as 10 mM stock solutions in DMSO and then diluted appropriately in serumless medium to final concentrations, e.g., 50, 500 and 5000 nM. Each concentration is assayed in triplicate.

[0051] Human recombinant IL-1 α (5ng/mL) (IL-1) is added to triplicate control wells and to each well containing drug. Triplicate control wells are also set up in which neither drug nor IL-1 are added. The medium is removed and fresh medium containing IL-1 and the appropriate drug concentrations is added on days 6, 12, 18 and 24 or every 3 - 4 days if necessary. The media removed at each time point is stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells has almost completely resorbed (about day 21), the experiment is terminated. The medium is removed and stored. Aliquots (100 μ l) from each well at each time point are pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot.

Variation 2

[0052] The experimental set-up is the same as outlined above in Variation 1, until day 12. On day 12, the conditioned medium from each well is removed and frozen. Then one ml of phosphate buffered saline (PBS) containing 0.5 μ g/ml trypsin is added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution is removed. Aliquots (50 μ l) of the PBS/trypsin solution and the previous two time points (days 6 and 12) are pooled, hydrolyzed and hydroxyproline content determined. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot. In this variation, the time course of the experiment is shortened considerably. The addition of trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that has been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment produces only low background levels of collagen degradation in the cartilage explants.

[0053] The data for Examples 1-3 in the cartilage explant assay are summarized in Table 3. For comparison, their IC₅₀'s versus type I collagen are also included. It can be seen from Table 3 that inhibition of type II cartilage collagen degradation correlates very well with inhibition of MMP-13 but not at all with inhibition of MMP-1. Thus, not only does the inhibitory profile of the active collagenase in the conditioned medium correlate with MMP-13 inhibition, inhibition of IL-1 induced type II cartilage collagen degradation also correlates with MMP-13 inhibition.

TABLE 3

Example	MMP-1 Type I Collagen IC ₅₀ (nM)	MMP-13 Type I Collagen IC ₅₀ (nM)	Cartilage Conditioned medium IC ₅₀ (nM)	Cartilage Explant Assay IC ₅₀ (nM)	Cartilage Explant Assay IC ₅₀ (nM)
1	3.5	1.5	10	Variation 1 60*	Variation 2 50
2	22000	52	220	900**	550
3	40000	40	400		890

* Average IC₅₀ (variation 1 and 2) Example 1 = 90 ± 35 nM** Average IC₅₀ (variation 1 and 2) Example 2 = 725 ± 400 nM.

[0054] For administration to mammals, including humans, for the inhibition of matrix metalloproteinases, a variety of conventional routes may be used including oral, parenteral (e.g., intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the active compound will be administered at dosages between about 0.01 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

[0055] The active compounds can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight

[0056] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

[0057] For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

[0058] The active compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0059] For intranasal administration or administration by inhalation, the active compounds are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Claims

1. Use of a collagenase-3 selective inhibitor or a pharmaceutically acceptable salt in the preparation of a medicament for the treatment or prophylaxis of a disorder or condition which can be treated or prevented by selectively inhibiting collagenase-3.
2. Use as claimed in claim 1 wherein the medicament can treat said condition or disorder without producing systemic connective tissue toxicity.
3. Use as claimed in claims 1 or 2 wherein the condition or disorder is osteoarthritis.
4. Use as claimed in any one of claims 1 to 3 wherein the collagenase-3 inhibitor is selected from the group consisting of;

1-([4-(4-fluorophenoxy)benzenesulfonyl]-pyridin-3-ylmethylamino)-cyclopentanecarboxylic acid,
2-([4-(4-fluorophenoxy)benzenesulfonyl]-pyridin-3-ylmethylamino)-N-hydroxy-2 methyl-propionamide,

(4-benzyl-benzyl)-[2-(2,2-dimethyl-1-methylcarbamoylpropylcarbamoyl)-6-phenoxy-hexyl]-phosphinic acid,
 2-amino-3-[4-(4-fluorophenoxy)benzenesulfonyl-N-hydroxypropionamide,
 N-hydroxy-2-[(4-phenoxy-benzenesulfonyl)-pyridin-3-ylmethylamino]-acetamide,
 (4-benzyl-benzyl)-(2-[2-(4-methoxy-phenyl)-1-methylcarbamoylethylcarbamoyl]-6-phenoxy-hexyl)-phosphin-
 ic acid,
 3-[4-(4-fluorophenoxy)benzenesulfonyl]-2, N-dihydroxypropionamide,
 2-[1-[4-(4-fluorophenoxy)benzenesulfonyl]-cyclobutyl]-2, N-dihydroxy-acetamide,
 3-(4-phenoxybenzenesulfonyl)-7-oxa-bicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide,
 2-[4-(4-fluorophenoxy)benzenesulfonyl-amino]-N-hydroxy-2-methyl-propionamide,
 1-[4-(4-fluorobenzoyloxy)-benzenesulfonyl]-2-hydroxycarbamoylpiperidine-4-carboxylic acid
 4-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl]-4-oxobutyric acid,
 4-[4-(4-chlorophenoxy)benzenesulfonylmethyl]-tetrahydropyran-4-carboxylic acid hydroxyamide,
 (S)- α [2-(4'-chloro[1,1'-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1, 3-dioxo-2H-isoindole-2-butanoic acid;
 4-[4-(4-chlorophenoxy)phenylsulfonylmethyl]-tetrahydropyran-4-(N-hydroxycarboxamide), and
 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxam-
 ide,

or a pharmaceutically acceptable salt thereof.

(19)



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(54) **The use of MMP-13 selective inhibitors for the treatment of osteoarthritis and other matrix metalloproteinase-mediated disorders**

(57) The present invention relates to the use of matrix metalloproteinase-13 selective agents for the treat-

ment or prevention of osteoarthritis and other matrix metalloproteinase-mediated disorders.

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Application Number

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Y		1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search	Date of completion of the search	Examiner	
MUNICH	7 August 2000	Brunnauer, H	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>Q : non-written disclosure</p> <p>P : intermediate document</p>			



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INCOMPLETE SEARCH
SHEET C

Application Number
EP 98 30 8563

Claim(s) searched completely:

4

Claim(s) searched incompletely:

1-3

Reason for the limitation of the search:

Present claims 1-3 relate to the use of an extremely large number of compounds defined by reference to desirable characteristic or property, namely to the use of collagenase-3 selective inhibitors for treating corresponding disorders.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as disclosed in claim 4 and on page 4-5 of the description.



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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 98 30 8563

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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Y	<p>REBOUL P. ET AL: "New Collagenase-3, is expressed and synthesized by human Chondrocytes but not by Synoviocytes"</p> <p>J.CLIN.INVEST.,</p> <p>vol. 97, 1996, pages 2011--2019,</p> <p>XP000916946</p> <p>* abstract *</p> <p>* page 2017, left-hand column *</p>	1-4	<p>TECHNICAL FIELDS SEARCHED (Int.Cl.6)</p>

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 98 30 8563

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82